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SPONTANEOUS HYPOGLYCEMIA DUE TO ATROPHY OF THE ADRENAL GLANDS

REPORT OF A CASE

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It has been established that hypoglycemia may be due to a variety of causes. In some cases disturbance of the islets of Langerhans, such as hyperplasia,[1] adenoma [2] or carcinoma,[3] has been responsible. In other instances disease of the liver [4] or insufficiency of the pituitary body [5] or

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1. Gray, S. H., and Feemster, L. C.: Compensatory Hypertrophy and Hyperplasia of the Islands of Langerhans in the Pancreas of a Child Born of a Diabetic Mother, Arch. Path. **1**:348-355 (March) 1926. Harris, S.: Hyperinsulinism: A Definite Disease Entity, J. A. M. A. **101**:1958-1965 (Dec. 16) 1933.

2. Whipple, A. O., and Frantz, V. K.: Adenoma of Islet Cells with Hyperinsulinism, Ann. Surg. **101**:1299-1335 (June) 1935. Womack, N. A.; Gnagi, W. B., Jr., and Graham, E. A.: Adenoma of the Islands of Langerhans with Hypoglycemia: Successful Operative Removal, J. A. M. A. **97**:831-836 (Sept. 19) 1931.

3. Cragg, R. W.; Power, M. H., and Lindem, M. C.: Carcinoma of the Islands of Langerhans with Hypoglycemia and Hyperinsulinism, Arch. Int. Med. **60**:88-99 (July) 1937. Wilder, R. M.; Allen, F. N.; Power, M. H., and Robertson, H. E.: Carcinoma of the Islands of the Pancreas: Hyperinsulinism and Hypoglycemia, J. A. M. A. **89**:348-355 (July 30) 1927.

4. (*a*) Briggs, J. F., and Oerting, H.: Extra-Pancreatic Hypoglycemia, Am. J. Digest. Dis. & Nutrition **3**:436-438 (Aug.) 1936. (*b*) Coller, F. A., and Jackson, H. C.: Surgical Aspects of Hypoglycemia Associated with Damage to the Liver, J. A. M. A. **112**:128-134 (Jan. 14) 1939. (*c*) Judd, E. S.; Kepler, E. J., and Rynearson, E. H.: Spontaneous Hypoglycemia: Report of Two Cases Associated with Fatty Metamorphosis of the Liver, Am. J. Surg. **24**:345-363 (May) 1934.

5. Foley, M. P.; Snell, A. M., and Craig, W. McK.: Anterior Pituitary Tumor Associated with Cachexia, Hypoglycemia, and Duodenal Ulcer, Am. J. M. Sc. **198**:1-8 (July) 1939.

of the adrenal glands [6] has given rise to severe and at times fatal hypoglycemic attacks. There have been reported numerous other explanations for hypoglycemia, such as lactation, muscular wasting, renal glycosuria, excessive fatigue and fasting.[7] These conditions only rarely produce severe symptoms. Because cases of severe spontaneous hypoglycemia of extrapancreatic origin are less frequently reported than cases of hypoglycemia due to islet cell changes, it is of interest to report a case in which the hypoglycemia is considered due to insufficiency of the adrenal glands.

REPORT OF CASE

The patient was admitted to the Rochester State Hospital on Feb. 7, 1939, with a history of mental trouble for the past seven years. She was 37 years old at the time of admission. The family history was significant in that one brother had committed suicide in a fit of depression and the mother had always been considered "queer" because of her suspicious, domineering manner.

The patient's birth and development were normal. She completed the eighth grade at the age of 15 and is said to have been a bright student. Her menstrual periods began at the age of 14 and were always normal. In 1923, at the age of 22, she was married. There were no pregnancies and no miscarriages or abortions. The past medical history was irrelevant except for "rheumatism" in 1931, which subsided after tonsillectomy in the same year. The patient worked as a stenographer from 1923 until 1932, when she lost her position "because of lack of employment."

In 1932 a change in her personality was noted. She formerly had been an efficient stenographer and had managed her home besides, but she no longer had any interest in her housework and did it very poorly. She began to think that persons were talking about her and spying on her. During the next seven years it was necessary for the family to change residence four times because of the trouble she caused as a result of these ideas. Her paranoid delusions gradually became more prominent, but no striking change was noted until 1938, when she began to have "mean spells." Such spells were of one to two days' duration. During them she would be excited, overactive, irritable and at times violent. Her memory for these spells was good, and she would at times apologize for her behavior. There were no episodes resembling clouded states or convulsions and no periods of unconsciousness. Her husband did not recall that these spells were related to periods of fasting or were relieved by taking food. He admitted that during the past year she had manifested an unusual desire for sweets. During this time her paranoid ideas extended to include her own family and her husband. Strangely enough, she trusted and confided in her mother-in-law. Her mental condition finally necessitated commitment to the Rochester State Hospital.

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6. (*a*) Anderson, I. A., and Lyall, A.: Addison's Disease Due to Suprarenal Atrophy with Previous Thyrotoxicosis and Death from Hypoglycemia, Lancet **1**:1039-1043 (May 1) 1937. (*b*) Welty, J. W., and Robertson, H. F.: Hypoglycemia in Addison's disease, Am. J. M. Sc. **192**:760-764 (Dec.) 1936. Briggs and Oerting.[4a]

7. Wauchope, G. M.: Critical Review: Hypoglycemia, Quart. J. Med. **2**: 117-156, 1933.

On admission she was somewhat undernourished and pale. Her height was 5 feet 4 inches (162.5 cm.), her weight 114 pounds (51.7 Kg.) and her blood pressure 100 mm. of mercury systolic and 70 mm. diastolic. The results of physical and neurologic examinations were otherwise negative. There was no abnormal pigmentation of the skin or of the buccal mucous membranes. The erythrocyte count was 3,800,000 and the leukocyte count 5,200 in each cubic millimeter of blood, and the value for hemoglobin (Sahli) was 74 per cent. The voided specimens of urine were normal except for a few leukocytes. The Wassermann reaction of the blood was negative.

During the first two weeks in the hospital the patient was seclusive, asocial and negativistic. She expressed many paranoid delusions and had both auditory and visual hallucinations. She often had to be coaxed to eat. A diagnosis of dementia praecox of the paranoid type was made. One day she refused to eat her evening meal because of the belief that it was poisoned. On the following morning she became weak and confused and soon passed into unconsciousness. She was pale and sweaty, and the rectal temperature was 94.6 F. The value for blood sugar was found to be 70 mg. and that for blood urea nitrogen 20 mg. per hundred cubic centimeters. After approximately thirty minutes she spontaneously

TABLE 1.—*Blood Sugar During Dextrose Tolerance Test*

Time	Blood Sugar, Mg. per 100 Cc.
Fasting	67
½ hour after dextrose	125
1 hour after dextrose	148
2 hours after dextrose	142
3 hours after dextrose	129

recovered consciousness and subsequently took food. On the following day she again refused food and again became confused, weak and stuporous. At that time the value for blood sugar was 66 mg. per hundred cubic centimeters. A short time after being forced to drink orange juice, she recovered. During the following week two estimations of the value for blood sugar, made before breakfast, were respectively 80 and 90 mg. per hundred cubic centimeters.

One morning she was found cold, pale and sweaty and could not be aroused. The rectal temperature was 94.8 F.; the pulse rate 80 per minute, and the pulse was regular. The blood pressure was 80 mm. of mercury systolic and 60 mm. diastolic. Periodically there was breathing of the Cheyne-Stokes type. Occasional generalized tonic convulsive seizures occurred, lasting one to two minutes. The tendon reflexes were markedly hypoactive, and there was a bilateral Babinski sign. There were wandering movements of the eyes, with a horizontal nystagmus toward the left. At that time the level of blood sugar was 40 mg. and that for blood urea nitrogen was 18 mg. per hundred cubic centimeters. After intravenous injection of 20 cc. of 50 per cent dextrose solution she promptly recovered consciousness.

In an effort to prevent any more serious hypoglycemic episodes the patient was given a high carbohydrate diet, divided into eight small feedings during the twenty-four hours. At this time a roentgenogram of the head was made, which was normal. Three days later a dextrose tolerance test was carried out. After a fourteen hour fast, 50 Gm. of dextrose was given by mouth. The values for blood sugar are given in table 1.

An attempt was made to induce an attack by depriving the patient of food. Estimations of the level of blood sugar were made at intervals during a period of forty hours. At the end of that time the patient was stuporous and had to be revived by the intravenous injection of dextrose. The blood sugar levels during this test are given in table 2. During the time this test was in progress, a bromsulfalein test of hepatic function was made. There was grade 0 retention of dye, indicating normal hepatic function as far as that test was concerned. A few days later an insulin tolerance test was performed. After the patient had fasted for twelve hours, blood was drawn for a sugar estimation, and 4.7 units of insulin was given intravenously (0.1 unit per kilogram of body weight). The level of blood sugar was ascertained at intervals of fifteen minutes. The results of the test are given in table 3.

These attacks of unconsciousness, therefore, appeared to be definitely associated with periods of hypoglycemia, but except for unusual sensitivity to injected insulin

TABLE 2.—*Blood Sugar During Starvation*

Hours After Last Meal	Blood Sugar, Mg. per 100 Cc.
15	71
19	67
23	65
28	54
40	31

TABLE 3.—*Results of Insulin Tolerance Test*

Time	Blood Sugar, Mg. per 100 Cc.	Comment
9:25 a. m.	90	Given insulin
9:40 a. m.	62	
9:55 a. m.	45	Drowsy and complained of hunger
10:00 a. m.	..	Crying; restless; sweaty
10:10 a. m.	34	Flushed, stuporous and restless; given intravenous dextrose and recovered promptly

our investigations had yielded no evidence pointing to any of the extrapancreatic causes which are known to induce a lowering of the level of blood sugar. Therefore an abdominal exploration was carried out by one of us (Stalker) with the hope that a pancreatic tumor might be found and removed. We were unable to find any tumor or abnormality in the entire gland. The small intestine was examined for aberrant pancreatic tissue, but none was found. The liver and gallbladder were normal. Both kidneys were palpated, and no adrenal tumor could be felt. The question of resecting a portion of the pancreas was seriously considered, but because of the type of patient and her poor general condition it seemed inadvisable. However, in an attempt to bring about, with a minimum of risk, some reduction in secretion and partial atrophy of the gland, the pancreas was transligated at the junction of the proximal one-third and the distal two-thirds. Because of the preexisting anemia, the patient was given a transfusion of 500 cc. of blood immediately after the operation.

During the first twenty-four hours after the operation the patient's condition appeared good. The blood pressure stabilized between 90 and 100 mm. of mercury systolic and 60 mm. diastolic. Estimations of the value for blood sugar were made every four hours, and at the end of twenty-five hours the level was 90 mg. per

hundred cubic centimeters. At this time the patient was given an intravenous injection of 1,000 cc. of 7.5 per cent dextrose in physiologic solution of sodium chloride over a period of two and one-half hours. Approximately an hour after completion of the venoclysis, she requested and was given water, which she drank without difficulty. A few minutes later she suddenly became stuporous, with stertorous respirations, and death occurred almost immediately.

Postmortem examination revealed in the pancreas small foci of necrosis in the region of the surgical ligature which had been placed around the pancreas between the head and the body. A white, firm nodule measuring 8 mm. in diameter was observed in the substance of the head of the pancreas. No extensive foci of fat necrosis were seen, and the operative site was in good condition. After a prolonged and unsuccessful attempt to find the adrenal glands in situ, the tissue overlying the kidneys was removed en masse and dissected. When all possible adipose tissue had been removed from the mass on the right side, a thin, semitranslucent sheet of connective tissue remained, and when this was held up to the

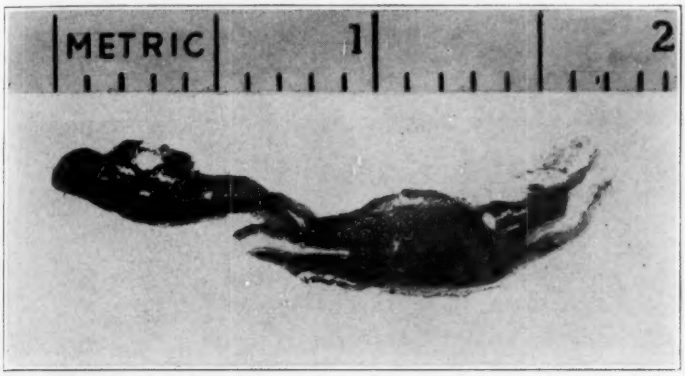

Fig. 1.—Right adrenal sectioned longitudinally (length, 16 mm.); × 5.

light a definitely outlined pale brown region could be distinguished. Sections through this region disclosed the fact that the brown tissue was slightly raised above the surface of the sheet of connective tissue, but at no point was it more than 3 mm. in thickness (fig. 1). A similar procedure with the mass of tissue above the left kidney revealed nothing which could be even tentatively identified as adrenal cortex. The liver was smooth and of normal color and consistency. The ovaries were small and cystic, and the thyroid gland appeared normal in size and shape but was unusually firm when compressed between the fingers. The thymus was almost entirely replaced by adipose tissue. The brain, including the pituitary and pineal bodies, revealed nothing grossly abnormal.

Sections for microscopic examination were taken from all organs, including numerous portions from the suspected adrenal tissue on the right and the mass of tissue above the left kidney. They were fixed in Orth's solution[8] and stained

8. A mixture of 10 parts of Müller's fluid and 1 part of solution of formaldehyde. Müller's fluid is a weak solution of potassium dichromate and sulfate.

with hematoxylin and eosin. Sections of the liver were frozen and stained with scarlet red.

The most remarkable observation was the state of the adrenal glands. The thin layer of brown tissue on the right proved to be markedly atrophied adrenal cortex with a thin zone of medulla still present (fig. 2*a*). A small number of the cortical cells in the zona glomerulosa retained their normal appearance and arrangement, but those of the fascicular and reticular zones were small and irregular, with pale-staining cytoplasm and eccentric nuclei. All the cells had completely lost the foamy appearance that is typically seen when they contain the usual amount of lipoids. The whole picture was one of gradual atrophy without signs of inflammation or replacement fibrosis. The medullary cells were pale

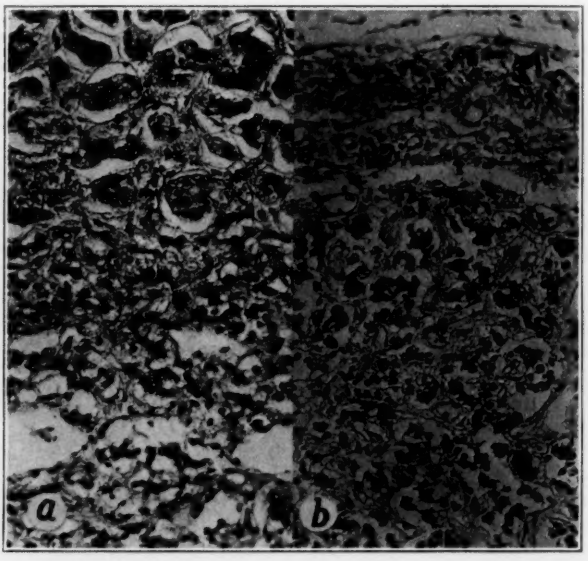

Fig. 2.—Right adrenal gland (*a*) and left adrenal gland (*b*), showing extreme atrophy of all cells; × 145.

and vacuolated, and the chromaffin reaction was negative. Fortunately, one of the blocks cut from the mass of tissue above the left kidney revealed remnants of adrenal cells (fig. 2*b*). They were more degenerated than those on the right side, but like them they were not associated with signs of inflammation or foci of necrosis, and only small amounts of fibrous connective tissue were present. Owing to the atrophic condition of these cells it was practically impossible to be certain whether they were cortical or medullary in origin. A rough estimate of the total amount of adrenal parenchyma placed it at 2 per cent of the normal.

Numerous sections taken from various regions of the pancreas revealed nothing particularly abnormal. The islands appeared small, but none of them were degenerated, and there were no large hyperplastic ones. The firm nodule

in the head of the pancreas proved to be merely a mass of fibrous tissue containing a few ducts. Small regions of infarction with fat necrosis were seen surrounding the surgical ligature.

The sections of liver appeared normal, and, although we failed to obtain alcohol-fixed tissue for the glycogen stain, the almost complete absence of the characteristic foamy appearance in the cells made us feel that the amount of glycogen was small. The scarlet red stain revealed only minimal amounts of lipoid in the liver cells.

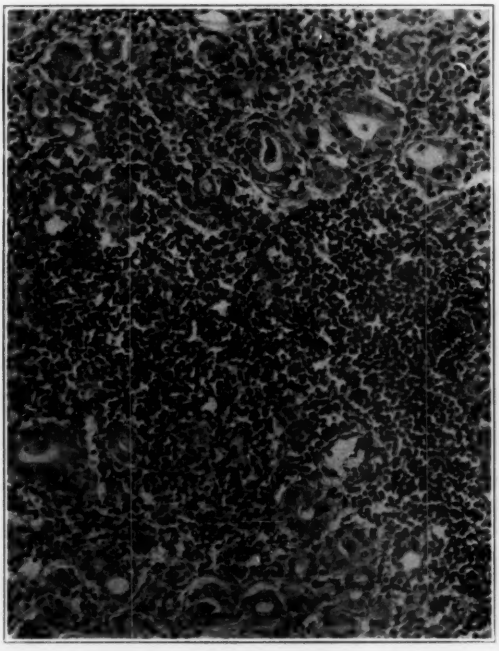

Fig. 3.—Hashimoto's thyroiditis; × 145.

The sections of the thyroid were of interest because they showed that the gross firmness of this gland was due to an extensive and intense degree of inflammation, the so-called Hashimoto's thyroiditis (fig. 3). The entire region was made up of enormous numbers of lymphocytes interposed between both hyperplastic and partially degenerated acini. Fibrous tissue was not abundant.

In sections the pituitary gland appeared normal. In the hypothalamus foci of degeneration were observed, similar to those seen by Moersch and Kernohan[9] in the brains of patients who died in a state of hypoglycemia.

9. Moersch, F. P., and Kernohan, J. W.: Hypoglycemia: Neurologic and Neuropathologic Studies, Arch. Neurol. & Psychiat. **39**:242-257 (Feb.) 1938.

COMMENT

The relation of the adrenal glands to carbohydrate metabolism has been, in recent years, the subject of considerable interest and investigation. Harrop and his co-workers [10] found that in adrenalectomized dogs given cortical extract or salt sufficient to maintain a normal salt and water balance hypoglycemia nevertheless developed if the dogs fasted. Long and Lukens [11] found that adrenalectomy ameliorates experimental diabetes in the cat. Himwich and his co-workers [12] showed that ligation of the lumboadrenal veins has a beneficial effect on experimental diabetes in both cats and dogs. The administration of large amounts of adrenal cortical extract tends to restore the diabetes of adrenalectomized-depancreatized animals.[13] Hypoglycemia is not a common finding in Addison's disease,[14] but in a limited number of cases severe hypoglycemic episodes are an outstanding feature.[6] In such cases the disturbance of salt and water metabolism may not necessarily parallel the disturbance of carbohydrate metabolism.[6a] Anderson [15] has reported a case of severe spontaneous hypoglycemia associated with a large carcinoma of one adrenal gland. In summary, we may say that the adrenal glands have an effect on carbohydrate metabolism which is antagonistic to that of insulin. When this effect is removed or sufficiently diminished, hypoglycemia may result.

Our patient had none of the cardinal symptoms of Addison's disease with the possible exceptions of low blood pressure and increased sensitivity to insulin. This is surprising in view of the small amount of adrenal tissue observed at postmortem examination. On two occasions, when the level of blood sugar was abnormally low, that of blood urea

10. Harrop, G. A.; Soffer, L. J.; Nicholson, W. M., and Strauss, M.: Studies on the Suprarenal Cortex: IV. The Effect of Sodium Salts in Sustaining the Suprarenalectomized Dog, J. Exper. Med. **61**:839-860 (June) 1935.

11. Long, C. N. H., and Lukens, F. D. W.: The Effects of Adrenalectomy and Hypophysectomy upon Experimental Diabetes in the Cat, J. Exper. Med. **63**: 465-490 (April) 1936.

12. Himwich, H. E.; Fazekas, J. F., and Martin, S. J.: The Effect of Bilateral Ligation of the Lumbo-Adrenal Veins on the Course of Pancreas Diabetes, Am. J. Physiol. **123**:725-731 (Sept.) 1938.

13. Long, C. N. H.; Fry, E. G., and Thompson, K. W.: The Effect of Adrenalectomy and Adrenal Cortical Hormones upon Pancreatic Diabetes in the Rat, Am. J. Physiol. **123**:130-131 (July) 1938. Lukens, F. D. W., and Dohan, F. C.: Further Observations on the Relation of the Adrenal Cortex to Experimental Diabetes, Endocrinology **22**:51-58 (Jan.) 1938.

14. Kepler, E. J., and Wilder, R. M.: Disturbances of Carbohydrate Metabolism Observed in Association with Tumors of the Adrenal Cortex, Acta med. Scandinav., 1938, supp. 90, pp. 87-96.

15. Anderson, H. B.: A Tumor of the Adrenal Gland with Fatal Hypoglycemia, Am. J. M. Sc. **180**:71-79 (July) 1930.

nitrogen was normal. The acute attacks which this patient suffered were entirely relieved by intravenous injection of small amounts of concentrated dextrose solution. Such treatment would have little or no beneficial effect on an acute crisis of Addison's disease. Nevertheless, we have assumed that adrenal insufficiency was the basic factor in the hypoglycemia. The symptoms manifested by the patient during the terminal crisis were different from those observed in previous attacks, and it is our impression that death was caused by a state of acute adrenal insufficiency. It seems unlikely that hypoglycemia contributed to her death, since the dextrose solution she was given should have been adequate to maintain the blood sugar at a normal level. The postmortem observation of extensive thyroiditis raises the question of whether hypothyroidism played a role in the hypoglycemic attacks. The patient showed none of the usual clinical symptoms of myxedema, and any hypothyroidism she had must have been very mild. As a rule, abnormally low values for blood sugar are not seen in cases of myxedema unless the disease is fairly advanced and even then are usually not accompanied by hypoglycemic symptoms. Therefore, we do not believe that the thyroiditis was of major importance in the development of the hypoglycemic attacks.

We believe that the psychosis in our patient was an independent disease and not a result of the hypoglycemia, even though it is well known that hypoglycemia may produce many types of abnormal mental symptoms.[16] However, an outstanding characteristic of these hypoglycemic symptoms is their episodic nature, with periods of normal behavior between attacks. The history of paranoid delusions and seclusive behavior would suggest that a schizophrenic process had been manifest for several years. Her unusual appetite and "mean spells" (which may have been mild hypoglycemic attacks) were of only one year's duration. Furthermore, during the periods when the level of blood sugar was known to have been low, she was somewhat confused and emotionally unstable.

The patient's mental condition precluded our obtaining any information concerning her subjective symptoms either before she came to the hospital or while she was under observation. For that reason, we had to depend on the physical findings and laboratory tests in our attempts to discover the cause of the hypoglycemia. The dextrose tolerance curve,

16. Greenwood, J., Jr.: Hypoglycemia as a Cause of Mental Symptoms, Pennsylvania M. J. **39**:12-16 (Oct.) 1935. Kepler, E. J., and Moersch, F. P.: The Psychiatric Manifestations of Hypoglycemia, Am. J. Psychiat. **94**:89-109 (May 14) 1937. Malamud, N., and Grosh, L. C., Jr.: Hyperinsulinism and Cerebral Changes: Report of a Case Due to Islet Cell Adenoma of the Pancreas, Arch. Int. Med. **61**:579-599 (April) 1938. Wilder, R. M.: Hyperinsulinism, Internat. Clin. **2**:1-18, 1933.

although abnormal in some respects, was of no material aid. The insulin tolerance test suggested that the patient was hypersensitive to this substance. This might have been interpreted as showing that one or more of the contrainsular factors was deficient but gave no clue as to which factor was at fault.

One of the most remarkable features of this case has been the apparent absence of any typical signs or symptoms of Addison's disease, even though the adrenal glands were almost completely atrophied. Had we but known of this atrophic state, a low sodium and high potassium diet might have aided materially in revealing the association of the hypoglycemia with adrenal insufficiency.

SUMMARY

The case has been described of a young woman suffering from spontaneous attacks of hypoglycemia. At operation, no tumor of the pancreas or any other cause could be found. Postmortem examination revealed extreme atrophy of both adrenal glands, and this is considered the cause of the hypoglycemia. Another finding which may possibly have influenced the metabolic disturbances was extensive inflammatory destruction of the thyroid, of the type described by Hashimoto.

HYPERTENSION (GOLDBLATT) AND UNILATERAL MALIGNANT NEPHROSCLEROSIS

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Experimental medicine usually receives its impetus from either clinical medicine or pathology. Thus, by the experimental production of lesions similar to those observed at autopsy, the reproduction of clinical symptoms, thought to be the result of organic changes, is often attempted. More rarely, perhaps, the investigator, without the definite support of clinical or pathologic observations, designs devices which when applied to the laboratory animal produce a definite complex of signs and symptoms. The results so obtained, however, cannot be applied to clinical medicine until a chance patient, dying from the same causes as the experimental animals, shows at postmortem examination conditions similar to those produced experimentally. The correlation with human pathology of results obtained from experimental work must await confirmation until by a "trick of nature" lesions identical to those experimentally produced are seen at postmortem examination.

Goldblatt's [1] experimental production of permanent arterial hypertension by clamping the renal arteries of the dog has found its corollary in human pathology. There are to date a few cases on record in which a "trick of nature" had produced constricting lesions either at the mouth of the renal artery or in the renal artery itself which, as far as could be judged, were responsible for permanent arterial hypertension in the patients. This communication is the result of a study of three patients, in all of whose cases a diagnosis of essential hypertension was made. The autopsy observations on all 3 showed, in the absence of bilateral arteriolonephrosclerosis, constricting lesions of one renal artery or its branches. In 2 of these the rare complication of unilateral malignant nephrosclerosis was found affecting the kidney whose arteries were not constricted. Of special interest is the fact that unilateral malignant nephrosclerosis could not be produced experimentally until recently, and its presence in the human being is, as far

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1. Goldblatt, H.: Experimental Hypertension Induced by Renal Ischemia, in Harvey Lectures, Baltimore, Williams & Wilkins Company, 1938, vol. 14, p. 523.

as we could ascertain, an extreme rarity. On the basis of Goldblatt's recent experimental work, malignant nephrosclerosis affecting only one kidney could easily be explained.

REPORT OF CASES

CASE 1.—A 46 year old white man, a waiter, complained of pain in the left upper quadrant of the abdomen, of five weeks' duration. He had been perfectly well until seven years previously, when he had symptoms typical of peptic ulcer. Under medical treatment he responded favorably and soon became asymptomatic. Two years later (1933) he sustained fractures of the skull and pelvis. After that time he "just didn't feel well" and complained of vague generalized discomfort. In 1936 he experienced dizziness severe enough to warrant medical attention and was told for the first time that he had "high blood pressure." The dizziness responded to medical care, but the hypertension persisted. A year prior to examination he snffered a fracture of the sternum in an automobile accident. Three months later he complained of dysuria, pain in the left lumbar region and hematuria lasting three days. A physician diagnosed "a passed renal stone." Five weeks before admission to the Michael Reese Hospital he noted pain in the left upper quadrant of the abdomen, which radiated to the epigastrium and to the right upper quadrant. The pain was cutting, constant and relieved by sedatives. There were no associated genitourinary or gastrointestinal symptoms. A loss in weight of 50 pounds (22.7 Kg.) occurred over a period of ten months.

On physical examination the patient appeared chronically ill and pallid. The lungs were clear except for a few rales at the base of the right and impaired resonance at the base of the left. The heart was enlarged; the sounds were of good quality, the rhythm was regular, and a blowing systolic murmur was heard over the entire precordium. The aortic and the pulmonic second sound were both accentuated. The arterial blood pressure in millimeters of mercury was 205 systolic and 140 diastolic. The edge of the liver was 2 fingerbreadths below the costal margin, and the liver was tender. Some tenderness was also elicited in the left upper quadrant of the abdomen, under the costal margin. No abnormal masses were felt in the abdomen. There was a slight tremor of the hands.

Laboratory Data.—The erythrocyte count varied between 3,330,000 and 4,840,000 per cubic millimeter. The value for hemoglobin ranged between 50 and 60 per cent; the leukocyte count, between 12,700 and 16,650 per cubic millimeter, with a normal differential count. The value for sugar was 58 mg., and that for nonprotein nitrogen ranged between 40 and 84 mg., per hundred cubic centimeters of blood. Repeated examinations of the urine revealed a specific gravity ranging between 1.003 and 1.015, with a 2 plus reaction for albumin and a few leukocytes but no red blood cells. The arterial blood pressure was persistently elevated and varied from 205 to 254 mm. of mercury systolic and 120 to 160 mm. diastolic.

Roentgen study revealed a suggestive mass in the left upper abdominal quadrant, which elevated the left leaf of the diaphragm. In addition, the crater of a duodenal ulcer was noted. An intravenous pyelogram showed no intrinsic changes in the genitourinary tract. The left renal outline was depressed downward. Bilateral ureteral catheterization for study of excretory function disclosed excellent excretion of dye on the left and fair excretion on the right within five minutes after intravenous injection. On retrograde pyelographic examination the left kidney was definitely depressed downward by an extrinsic mass located in the left upper quadrant.

Course.—The pain in the left upper quadrant of the abdomen persisted unabated, and the blood pressure maintained a high systolic and diastolic level. Gradually moderate dyspnea and orthopnea and slight edema of the ankles developed. At this time digitalization was started, but signs of moderate congestive heart failure persisted. Ten days before the patient died, he became slightly irrational; muscular twitchings were noted; the respiration was of the Biot type, and a friction rub was heard, localized beneath the lower part of the sternum. The nonprotein nitrogen content of the blood was 74 mg. per hundred cubic centimeters, and uremia was diagnosed. The course of the patient's illness during the last two weeks of hospitalization was rapidly downhill. For the three days before death the temperature, which had been normal previously, reached 102 F. daily. The clinical diagnosis was uremia, hypertensive cardiovascular renal disease, adrenal tumor and old peptic ulcer.

Postmortem Examination.—The more important observations were as follows: The body was emaciated, measuring 160 cm. and weighing 60 Kg. Both lower extremities showed a moderate degree of edema. The heart weighed 500 Gm., was enlarged and was displaced to the left. There was recent localized fibrinous pericarditis. The valvular apparatus was intact. The thickness of the left ventricle was 1.8 cm., and that of the right, 0.3 cm. The coronary arteries revealed a moderate degree of intimal thickening but were patent throughout. Both lungs were air containing and reddish brown and on pressure exuded an excessive amount of reddish, frothy fluid. There was no evidence of pneumonia. The liver was somewhat enlarged and was firmer than normal. On section it revealed large and depressed central zones. The spleen was enlarged and firm; the sectioned surface was purplish blue and presented an increase in trabecular markings.

The right kidney was firm and weighed 150 Gm. The capsule stripped with ease to reveal a uniformly and finely granular purplish gray surface speckled with punctate hemorrhagic areas measuring up to 3 mm. in diameter. The organ cut with normal resistance. On section the architecture of the cortex was obscured, and many red and gray dots were seen, in addition to minute foci of hemorrhages. The distinction between the cortex and the medulla was not well marked. The pelvis and ureter showed no changes. The right renal artery was widely patent throughout. There was no evidence of arteriosclerosis. The left kidney weighed 150 Gm. It was firmly attached to an overlying cystic retroperitoneal mass which seemed to replace the left adrenal gland. The kidney itself was of normal consistency. Its capsule stripped with ease to disclose a smooth and glistening slate gray surface which showed neither hemorrhages nor granules. In the region of the lower pole there was a yellowish depressed area measuring about 1 cm. in greatest dimension, which was sharply defined and which extended in the form of a wedge throughout the cortex. The organ cut with normal resistance, and on section the architecture of the cortex was clearly discernible. The demarcation between the cortex and the medulla was sharp. The pelvis and ureter showed no changes. The left renal artery was distinctly smaller than the right. Its orifice failed to admit a small probe. The vessel was markedly but incompletely obstructed by a firm, grayish, organized, partially calcified thrombus which extended over a distance of 1 cm., starting from a point about 0.2 cm. from the orifice of the vessel. Attached to the old thrombus was a more recent, adherent thrombus measuring about 1 cm., which almost completely occluded the lumen of the artery. The three terminal divisions of the left renal artery were widely patent and presented smooth intimal surfaces. The urinary bladder showed multiple single and confluent punctate hemorrhagic spots.

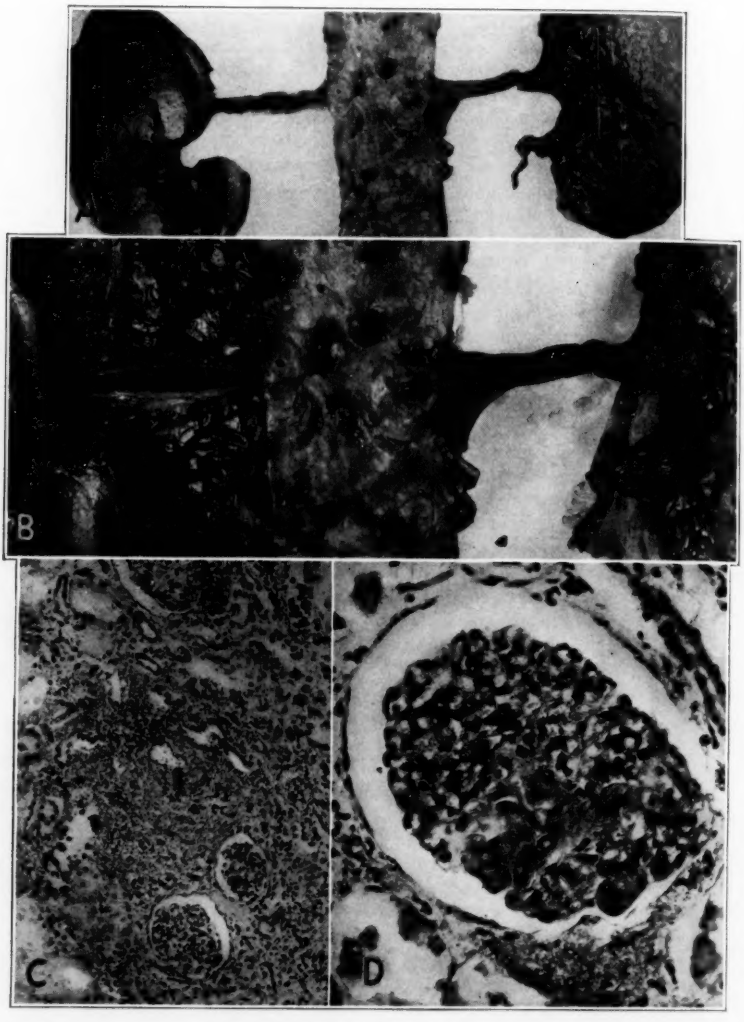

Fig. 1 (case 1).—*A*, aorta, renal arteries and kidneys (aorta opened posteriorly). Note the thrombus in the left renal artery, the smooth left kidney, the open right renal artery and the granular surface of the right kidney. (About ⅓ natural size.) *B*, thrombus in the left renal artery; note the granularity of the right kidney and the smooth left kidney (0.9 of natural size). *C*, histologic picture of the right kidney. Note the necrotic arteriole in about the center of the picture and the surrounding hemorrhage. (Iron hematoxylin and eosin preparation; × 84.) *D*, section of a glomerulus of the right kidney. Note the necrosis of some of the capillaries of the glomerulus. (Iron hematoxylin and eosin preparation; × 260.)

The right adrenal gland showed no changes. The left adrenal gland was practically replaced by a cystic tumor which on section proved to be an organized hematoma. At the periphery of the hematoma a small, thin rim of yellow adrenal cortical tissue could be recognized. The peripheral portions of the hematoma were completely organized and replaced by connective tissue. The adrenal arteries originated directly from the aorta. A probe inserted into the left adrenal vein opened into the hematoma.

The stomach presented thickened and enlarged rugae. A small stellate scar was noted on the lesser curvature and a similar one in the first third of the duodenum. Throughout the small and large intestines hemorrhagic discolorations were noted, varying from 2 to 3 cm. These were most marked in the cecum. A moderate deposit of fibrin was observed in these regions. The brain was edematous and showed flattened gyri. The entire circle of Willis disclosed moderate arteriosclerosis. Toward the outer portion of the globus pallidum a circumscribed area of hemorrhage was observed, measuring 0.5 by 1 cm. in its greatest dimensions.

Histologic Data.—Microscopic examination of the heart disclosed moderate fibrosis, particularly pronounced in the perivascular areas. The pericardium contained some fibrin and a few enmeshed polymorphonuclear leukocytes. The pulmonary alveoli were distended, their septums being frequently ruptured. Large, round mononuclear cells containing golden brown pigment granules were diffusely scattered throughout the alveoli. Sections of the liver revealed marked distention of the central veins and sinusoids with atrophy of the adjacent cords of liver cells. There was a moderate increase in periportal connective tissue. The lumens of numerous arterioles in the sections were distinctly narrowed by thickened and hyalinized walls. There were distended sinusoids in the spleen, and the walls of these were conspicuously thickened. Also, the small arteries and arterioles were markedly thickened and hyalinized.

The outstanding changes in the right kidney (with a widely patent main renal artery) were in the arterioles. Many of the arterioles had completely necrotic walls, the lumens of some of them being occluded by minute thrombi. Here and there arterioles were observed in the midst of a small area of hemorrhage. Often necrotic arterioles with hardly recognizable lumens were seen just entering glomeruli. Occasionally a few polymorphonuclear leukocytes were noted surrounding some of the arterioles. Severe hyalinization with marked constriction of lumens was noted in other arterioles. The glomeruli throughout were more cellular than normal. The capillaries of some of the glomeruli were necrotic, and intraglomerular hemorrhage was in evidence. Some of the convoluted tubules were dilated and presented granular cytoplasmic changes. Their lumens contained an albuminous precipitate. A number of arteries of the size of interlobular arteries presented marked intimal thickening, with reduplication of their elastic lamellae, and reduction in size of the lumens. In the left kidney (with an obstructed main renal artery) no histologic changes were noted. It must be particularly emphasized that the arterioles showed no changes. (The infarct described grossly was recognized histologically.)

The left adrenal gland showed cortical tissue adjacent to an old, organized hematoma with much hyalinized fibrous connective tissue containing calcific deposits. The arterioles of both glands presented moderate to severe intimal proliferation with hyalinization and narrowing of their lumens. The outstanding change in the pancreas was arteriolosclerosis. The submucosal arterioles in the gastrointestinal tract showed moderate to severe intimal proliferation and hyalinization. The brain revealed moderate to severe arteriosclerosis of the smaller arteries and a thrombosed artery in the region of the grossly described recent hemorrhage.

The main pathologic diagnoses were as follows: incomplete but marked thrombotic occlusions (old and recent) of the left renal artery; old, small infarct of the left kidney; unilateral malignant nephrosclerosis with arteriolonecrosis (right); localized, fibrinous pericarditis (uremic); hemorrhagic enterocolitis (uremic); edema of the brain (uremic) and recent focal hemorrhage into the right globus pallidum; old hematoma in the left adrenal gland; moderate to severe sclerosis of the arterioles of the spleen, liver, pancreas and intestines; hypertrophy and dilatation of the heart; chronic passive hyperemia of the lungs, liver, spleen and kidneys; edema of the lower extremities, and healed peptic ulcers (gastric and duodenal).

Summary.—A 46 year old man who sustained a fracture of the pelvis in an accident six years before death complained of spells of dizziness three years later, at which time arterial hypertension was first diagnosed. A year before death he was in an automobile accident, and three months later a tumor was recognized in the left retroperitoneal space. There was also an old history of peptic ulcer. During hospitalization the patient's blood pressure in millimeters of mercury varied from 205 systolic and 120 diastolic to 254 systolic and 160 diastolic. The nonprotein nitrogen content of the blood varied from 40 to 84 mg. per hundred cubic centimeters. Congestive heart failure gradually developed, and the patient died of uremia. Autopsy disclosed an organized thrombus in the left renal artery, but the left kidney showed no changes except a small infarct. The right kidney was the seat of arteriosclerosis of the larger arteries and typical malignant nephrosclerosis (arteriolonecrosis). There was also an old, organized hemorrhage in the left adrenal gland. Chronic passive hyperemia was present in the various organs.

Case 2.—A 35 year old woman complained of abdominal distress and vomiting for one month, during which time she had lost 25 pounds (11.3 Kg.) in weight. For the last few days diarrhea, with loose watery stools, had been present. Past history revealed that she had had "pyelitis" twelve years previously, severe headaches for over a year and visual disturbances for the past month. On physical examination the patient appeared acutely ill. The rectal temperature ranged between 101 and 102 F. There were marked pallor of the mucous membranes and a peculiar sallow tinge to the skin. The eyelids were puffy. The fundi revealed edema of the papillae, 4 plus. The arteries were practically invisible and apparently spastic. Numerous flame-shaped hemorrhage deposits were noted throughout the retina. The heart was enlarged to the left. There was a rough systolic murmur at the apex. The arterial blood pressure in millimeters of mercury was 224 systolic and 140 diastolic. Laboratory examination showed an erythrocyte count of 2,580,000 per cubic millimeter of blood, with a hemoglobin content of 50 per cent. The leukocyte count was 32,000 per cubic millimeter, with 94 per cent neutrophilic polymorphonuclear leukocytes. The value for blood chlorides was 425 mg. per hundred cubic centimeters. The value for nonprotein nitrogen initially was 78 mg. per hundred cubic centimeters and subsequently rose to 210 mg. The value for total protein was 6.2 per cent (albumin 4.3, globulin 1.9). The carbon dioxide–combining power was 36.2 volumes per cent. The value for creatinine was 12 mg. per hundred cubic centimeters. Examination of the urine

revealed a specific gravity ranging between 1.008 and 1.012. There was albumin (4 plus), and microscopically the urine was loaded with leukocytes, casts of various types and a few red blood corpuscles. The stools showed occult blood (4 plus). The patient's course continued progressively downhill. She became oliguric; a pericardial friction rub developed, and she died eight days after admission.

Postmortem Examination.—The more important observations were as follows: The body measured 168 cm. and weighed approximately 50 Kg. The pericardial cavity contained about 300 cc. of clear fluid and was partially obliterated by fibrinous adhesions, which were separated with ease. The loops of bowel were bound together by thin, fibrinous strands, which could be broken easily. The heart was enlarged, weighing 380 Gm., but otherwise showed no changes. The lungs, the liver and the spleen showed no changes of note.

The right kidney was much smaller than normal, weighing only 30 Gm. It was provided with three renal arteries, all of which arose from the aorta and individually supplied the midportion and the upper and lower poles. They measured respectively 1, 1.5 and 0.75 mm. in diameter. The lumen of the vessel supplying the midportion of the kidney was practically occluded by a thick, yellowish intimal plaque located about 5 mm. distal to the origin of the vessels. The remaining two main arteries were patent. The kidney itself was firmly adherent to the perinephric fat tissue and was somewhat firmer than normal. Its capsule stripped with ease to reveal a reddish tan, finely and coarsely granular surface with numerous reddish, flat scars of varying sizes. On section the cortex was reduced in size, and the line of differentiation between the cortex and the medulla was indistinct. The architecture of the cortex was seen more or less clearly, but the medulla in many portions could not be defined. The pelvis and calices were dilated. The upper calix contained three brownish black, firm, granular stones, measuring up to 1 cm. in their greatest diameter. The right ureter contained a small amount of yellowish turbid material (pus). The left kidney was slightly enlarged, weighing 160 Gm. The organ was somewhat softer than normal, and the capsule stripped with some difficulty to reveal a reddish granular surface speckled with minute and somewhat larger hemorrhagic areas. The organ cut with slightly diminished resistance. The normal striations of the cortex were everywhere clear, and many reddish and yellowish gray dots and streaks were seen. A few minute foci of hemorrhages were noted. The pelvis showed no changes. The left renal artery was of normal size and showed normal distribution. The left ureter contained a small amount of yellowish turbid material (pus). The wall of the urinary bladder was somewhat thicker than normal. The mucosa was thrown into folds, and a few hemorrhagic foci were noted.

The stomach showed a few hemorrhages in the mucosa but no other gross changes. The small and large intestines showed a number of flat ulcerated areas, some of which were covered with a pseudomembrane. Hemorrhagic foci were observed throughout the mucosa of the small and large intestines, particularly surrounding the ulcerated areas. In the region of the ulcers the peritoneal surfaces were covered with fibrin.

Histologic Study.—The heart muscle was unaltered. The pericardial surfaces contained much fibrin and a few enmeshed lymphocytes and polymorphonuclear leukocytes. The lungs revealed nothing unusual. The central veins and sinusoids of the liver were moderately dilated, and the liver cells throughout had a granular cytoplasm. The arterial tree was normal. The follicles in the spleen were ill defined, and the pulp showed no changes. The arterioles exhibited severe sclerotic changes, but there was no evidence of necrosis.

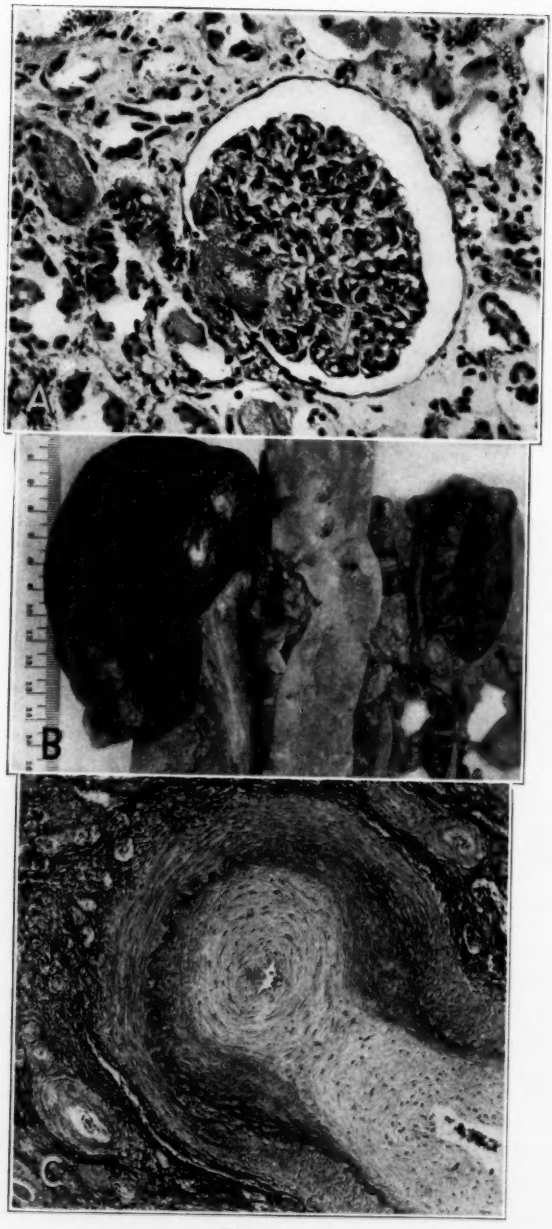

Figure 2

(See legend on opposite page)

Right Kidney (contracted kidney): The glomeruli were irregularly distributed. For the most part, they were completely transformed into fibrotic, hyalinized balls. Several of the normal-appearing glomeruli were encompassed by connective tissue rich in fibroblasts and lymphocytes. Many tubules were dilated, filled with hyaline casts and lined by flattened epithelial cells. Other tubules were small, apparently compressed by markedly increased, dense connective tissue. All large branches of the renal arterial tree presented marked intimal proliferation with hyalinization and severe restriction of their lumens. Many of these vessels revealed only slit-like openings. The arterioles were markedly sclerotic but showed no evidence of necrosis.

The most outstanding changes in the left kidney were observed in the arterioles. Some were severely hyalinized, their lumens practically occluded. The walls of a number of other arterioles were necrotic and their lumens either restricted by thickened walls or occluded by recent hyaline thrombi. Often ghostlike arterioles were seen entering a glomerulus. Occasionally intraglomerular capillaries were also necrotic. Focal hemorrhages and occasional polymorphonuclear leukocytes were noted surrounding several arterioles. In a few glomeruli early fibrotic changes were noted, and the tubules between these glomeruli were atrophic or replaced by connective tissue, which was sparsely infiltrated with lymphocytes. Many glomeruli showed no intrinsic pathologic changes, although occasionally red blood corpuscles were found in their capsular spaces. Some of the tubules were dilated and their lining cells markedly granular. Some tubules contained an amorphous neutrophilic precipitate, others red blood corpuscles and still others a few polymorphonuclear leukocytes. The last-mentioned type of exudate was particularly noted in the collecting tubules. The interstitium showed an excess of dense fibrous connective tissue in which were seen lymphocytes, plasma cells and foci of polymorphonuclear leukocytes. Only slight arteriosclerotic changes were seen in the larger arteries.

There were no histologic changes in the adrenal glands other than a moderate degree of arteriosclerosis of the capsular vessels. Sections taken from the gastrointestinal tract disclosed large foci of necrosis with regions of hemorrhage. Much fibrin with enmeshed polymorphonuclear leukocytes was seen covering denuded regions of the mucosa. In the arterioles of the submucosa a distinct intimal thickening with hyalinization and narrowing of the lumens was noted, but no necrotic arterioles were recognized. The serosa was covered with fibrin and enmeshed polymorphonuclear leukocytes.

The main pathologic diagnoses were: unilateral (right) pyelonephritic contracted kidney, with nephrolithiasis; multiple renal arteries (three) with severe arteriosclerotic constriction of the lumen of one of them and advanced obliterative intrarenal arteriosclerosis; unilateral (left) recent acute pyelonephritis with superimposed early malignant nephrosclerosis (arteriolonecrosis); hypertrophy of the heart, main part of the left ventricle; acute ulcerative enterocolitis; acute fibrinopurulent peritonitis, and acute fibrinous pericarditis.

Fig. 2.—*A* (case 1), histologic picture of right kidney. Note the necrotic vas afferens. (Iron hematoxylin and eosin preparation; × 200.) *B* (case 2), kidneys. Note the small right kidney (pyelonephritic contracted kidney) and the larger left kidney (with malignant nephrosclerosis). *C* (case 2), histologic picture of the right kidney. Note the arteriosclerosis with severe narrowing of the lumen of an intrarenal artery. (Iron hematoxylin and eosin preparation; × 56.)

Summray.—In a 35 year old woman who had suffered an attack of "pyelitis" twelve years before death marked hypertension gradually developed and she died in uremia. Autopsy disclosed a unilateral pyelonephritic contracted kidney and malignant nephrosclerosis with acute pyelonephritis of the contralateral kidney.

CASE 3.—On his first admission to the hospital a 60 year old white man complained of vague gastrointestinal symptoms and headaches. Mental and psychic changes had been noted by relatives during the past year. There was a history of hypertension of about one year's duration. Physical examination revealed peripheral arteriosclerosis, emphysema and a slightly enlarged heart. The arterial blood pressure in millimeters of mercury was 172 systolic and 100 diastolic. Fundoscopic examination disclosed narrowed arteries and "silver-wired" vessels but no hemorrhage or exudate. Laboratory study revealed complete achlorhydria. The urine gave a 1 plus reaction for albumin and ranged in specific gravity from 1.006 to 1.008. The value for nonprotein nitrogen was 33 mg. and that for sugar 76 mg. per hundred cubic centimeters of blood. The patient remained in the hospital for fourteen days and was discharged unimproved.

The second admission was one month later. The patient had been found in bed, unable to speak, although he attempted to move his lips. Similar transient episodes were reported by the family. In addition, twitchings of his left extremities were noted.

Physical Examination.—Cheyne-Stokes respiration was observed. The patient was unable to speak but able to follow instructions. Neurologic examination disclosed rapidly changing signs. The deep reflexes were always present, and the Babinski sign and its confirmatory signs were absent. Rales were heard throughout all lobes of the lungs, but the resonance was normal. The heart showed no abnormalities; the rhythm was regular at 68 beats per minute. The arterial blood pressure was in excess of 260 mm. of mercury systolic and 130 mm. diastolic. The urine showed no sugar, a 4 plus reaction for acetone and a faint trace of albumin. The patient lapsed into coma and died within eleven hours.

Postmortem Examination.—Only the more important observations are given. The body measured 158 cm. and weighed about 65 Kg. The right pleural cavity was obliterated by adhesions. The remainder of the serous cavities showed no changes. The heart weighed 400 Gm. The valvular apparatus showed no changes except a moderate degree of arteriosclerosis of the mitral and aortic valves. The myocardium was firm and brownish gray and showed a number of grayish streaks throughout. The left ventricle measured 1.5 cm. and the right 0.2 cm. in thickness. There were severe sclerosis of the coronary arteries, a moderate degree of arteriosclerosis of the thoracic aorta and severe sclerosis of the abdominal aorta. Both lungs were emphysematous and showed areas of bronchopneumonia. The liver revealed a moderate degree of chronic passive hyperemia.

The right kidney weighed 225 Gm. and was larger than normal. Its capsule stripped with ease to reveal a finely and uniformly granular surface. The granules were slate gray and were separated from one another by minute, depressed reddish scars. The organ cut with increased resistance to disclose a well defined cortex and medulla. The cortex was larger than normal, and its striations were clearly recognized. The right pelvis and ureter showed no changes. The right renal artery was widely patent.

The left kidney was much smaller than normal, weighing 50 Gm. It was markedly contracted and densely adherent to the perirenal fat, from which it was

inseparable. A large cyst filled with clear, yellow fluid occupied its upper pole. The capsule stripped with great difficulty and revealed a very irregular granular surface. The granules were separated from one another by a number of scars, some of which were flat and reddish. Others were deep and varied from 2 to 8 mm. in their greatest dimension. The organ cut with great difficulty and grittiness. The cortex was reduced in size, and the architecture was obscured. In some portions only a small rim of cortical tissue could be discerned. The pyramids were also reduced in size, and some of them contained calcareous material. The boundary between the cortex and the medulla was indistinct. The renal pelvis was somewhat dilated. The left ureter was thickened, and its lumen was markedly narrowed. Hyalinized and calcified intimal plaques of the aorta in the region of the orifice of the left renal artery produced great constriction of its mouth. The renal artery itself showed thickened and partially calcified walls, but the lumen of the vessel was patent.

There was severe arteriosclerosis of the vessels of the base of the brain. Multiple sections of the brain showed no gross abnormality.

Histologic Study.—The outstanding histologic change in the myocardium was a moderate increase in perivascular connective tissue. Only occasionally was focal replacement of muscle fibers by fibrous connective tissue observed. The fibers of the heart muscle seemed larger than normal. There were intimal thickening and narrowing of the lumens of all divisions of the coronary arteries. There was typical, though early, bronchopneumonia. The bronchial lumens were studded with polymorphonuclear leukocytes. Sections of the liver revealed slight dilatation of the central veins and moderate cloudy swelling of the hepatic cells. There was distinct intimal thickening of the arterioles with narrowing of their lumens. Excessive sclerosis and hyalinization with consequent marked narrowing of channels were noted in the arterioles of the spleen.

In the left kidney (with an obstructed main renal artery) only a few normal glomeruli were seen. Many of the glomeruli were hyalinized and apparently drawn together, and the intervening tubules had completely disappeared or were replaced by connective tissue. Some tubules were dilated and filled with a finely granular eosinophilic material or were small and apparently compressed by newly formed connective tissue. There was little cellular infiltration, and only occasional accumulations of lymphocytes were noted. Throughout the section, marked intimal proliferation with consequent severe reduction of the lumens of all the arteries the size of the arcuate arteries was observed, in addition to multiplication of their internal elastic lamellae. There was also marked thickening of the intima of the arterioles. The capillaries throughout were dilated and filled with red blood corpuscles. Here and there small papillary adenomas were seen.

The glomeruli of the right kidney (with a patent main renal artery) were not conspicuously altered. A slight granularity of the cytoplasm of the lining cells of the tubules was noted. Several larger arteries had hyalinized and thickened intima, and the medium and small arteries were only moderately sclerosed, without restriction of the lumens. The arterioles presented distinct but not advanced sclerosis.

Sections of the adrenal glands revealed distinct arteriolosclerosis, particularly pronounced in the capsular region. The brain was the seat of severe arteriosclerosis of all the small vessels, and a number of areas of malacia could be discerned.

The relevant pathologic diagnoses were: generalized arteriosclerosis, notably involving the aorta, the left renal artery, the coronary arteries and the cerebral

arteries; severe stenosis of the lumen of the left renal artery; pyelonephritic and arteriosclerotic contractions of the left kidney; compensatory hypertrophy of the right kidney; hypertrophy of the heart; myocardial fibrosis; bronchopneumonia, and encephalomalacia.

Summary.—A 60 year old patient who had had known hypertension for a year died as a result of bronchopneumonia after he had been the victim of a cerebral accident. Autopsy revealed generalized arteriosclerosis, encephalomalacia, marked arteriosclerotic stenosis of the left renal artery and unilateral severe pyelonephritis and arteriosclerotic contraction of the kidney. The right kidney showed simple compensatory hypertrophy.

COMMENT

These 3 patients are similar in that all had marked arterial hypertension. Two died in uremia and 1 of bronchopneumonia. The autopsy disclosures at first were perplexing because of the contrasting findings in the two kidneys in all 3 instances. From the clinical observation, arteriolosclerosis of both kidneys (nephrosclerosis of the arteriolar variety) was expected, as this lesion is often a verification of the diagnosis of essential hypertension. Because of the fact that 2 patients died in uremia, the possibility of superimposed arteriolonecrosis of the kidneys was considered. The first 2 cases are particularly noteworthy, since in both unilateral renal arteriolonecrosis (malignant nephrosclerosis) was encountered.

It would have been extremely difficult, perhaps impossible, to correlate the clinical and pathologic findings in these instances, especially in the first 2, had it not been for the recent investigations pursued by Goldblatt and others, who were able to produce permanent arterial hypertension in the experimental animal. It may be recalled, in short, that in their experiments gradual constriction of both renal arteries of the dog resulted in permanent arterial hypertension. If only one renal artery was constricted, the arterial blood pressure gradually rose, reaching a certain high level, but later returned to the neighborhood of the original basic level. Only in an occasional dog did arterial hypertension persist for months after the renal artery of only one side had been damaged. It was found in these experiments that in animals in which hypertension without accompanying renal excretory insufficiency had existed for several years the arterioles in many structures and organs, except the ischemic kidneys, had thickened walls, owing to hypertrophy of the media. There was no thickening or hyalinization of the intima of these vessels in any organ except the eye. In the retinas of some of the animals, in which significant renal excretory disturbance had not been detected, the arterioles did show signs of sclerosis. In the further pursuit of his work, Goldblatt [2] found that in those instances

2. Goldblatt, H.: Studies on Experimental Hypertension: VII. The Production of the Malignant Phase of Hypertension, J. Exper. Med. **67**:809, 1938.

in which constriction of both renal arteries was made very great from the beginning, there resulted arterial hypertension complicated by renal excretory insufficiency and uremia and at autopsy necrosis of the arterioles was observed in many organs (except the kidneys). Goldblatt [3] further found that if only one renal artery was clamped and (after development of the arterial hypertension) the ureter of the contralateral kidney was ligated, the dog had uremia. Autopsy on these dogs disclosed that the arterioles of many organs and also of the kidney whose artery was unobstructed but whose ureter was ligated showed typical arteriolonecrosis. These changes were similar in all respects to those observed in the acute malignant phase of essential hypertension in man (malignant nephrosclerosis). Goldblatt has concluded that in the dog both hypertension and severe disturbance of renal excretory function are necessary for the production of arteriolonecrosis. Bilateral sudden excessive constriction of the main renal arteries results in the development of hypertension and uremia and of arteriolonecrosis in many organs, but not in the ischemic kidneys. In order to produce this lesion in at least one kidney it is necessary greatly to constrict one main renal artery and to occlude the ureter of the contralateral kidney. In the latter, the arteriolonecrosis develops. By both methods hypertension and renal excretory insufficiency are produced. Since hypertension is not present within the arterioles of the kidney whose artery is constricted, arteriolonecrosis does not develop in this kidney but may be present in other organs and also in the opposite kidney, whose ureter has been ligated but whose circulation is intact so that the vascular tension may be increased in this organ.

Knowledge of this experimental work is indispensable for the understanding of the first 2 cases reported in this paper, in both of which there was unilateral malignant nephrosclerosis (arteriolonecrosis). The first instance is particularly interesting because it represents in the human being the exact counterpart of Goldblatt's experiment. In the light of these experiments the essentials of the patient's history may be reviewed as follows: The patient was well until he sustained a pelvic fracture, after which he "just did not feel well" and subsequently was told for the first time that he had high blood pressure. From the observations at autopsy it seems probable that as a result of the accident he sustained an injury not only to the pelvic bones but to the left renal artery. Because of the injury to this artery a thrombus gradually formed. At autopsy it was observed that the thrombus in parts was very old, calcified and fibrosed. The thrombus gradually grew by apposition and led to severe, yet incomplete, constriction of the lumen of this artery. Thus a process ensued equivalent to Goldblatt's clamping of one main renal artery. Whatever caused the rise in arterial

3. Personal communication to the authors.

pressure in Goldblatt's experiment caused the rise in arterial pressure in our patient. The thrombus of the renal artery surely could not have completely occluded the artery, or, if it did, there was considerable accessory circulation to the kidney, since on gross and histologic examination it was found to be, in general, normal. Only a small infarct was present, which must be related to the partial thrombosis of the renal artery.

From the foregoing description it is evident that the accident, with the resulting thrombus in the renal artery, was responsible for the gradually developing arterial hypertension. Perhaps at the time of his first accident the patient also had sustained an injury to the left adrenal vein. As a result of the second accident a rupture of the left adrenal vein ensued, leading to hemorrhage into the adrenal gland. This hemorrhage, however, was purely incidental and had nothing to do with the death of the patient. Clinically, however, it played an important role, since the enlarged adrenal gland produced pain, could be palpated and was visible on pyelographic study. The enlarged adrenal gland had been diagnosed as an adrenal tumor.

As a result of the permanent marked arterial hypertension the heart gradually enlarged, and signs of congestive heart failure eventually developed, as was evidenced by the enlarged and painful liver and the swelling of the lower extremities. At that time the nonprotein nitrogen content of the blood began to rise, and the patient soon thereafter showed signs of uremia. The friction rub over the precordium was interpreted as indicating uremic pericarditis. With the onset of congestive heart failure the patient's kidneys apparently could not function properly, and excretory renal insufficiency set in. With the development of the sluggish state associated with congestive heart failure, the renal blood flow diminished steadily and markedly to the point of producing prerenal azotemia. The ultimate effect of this diminished renal blood flow was exactly the same as that of further mechanical constriction of the renal arteries and impairment of excretory function in the experimental dog. By these circumstances the second factor necessary for production of the malignant phase of hypertension was introduced; namely, renal excretory insufficiency. Autopsy disclosed the arteriolonecrosis and the accompanying acute periarteritis and endarteritis which are characteristic of malignant nephrosclerosis. However, these changes were found in but one kidney, the kidney whose main artery had been patent. These findings are in complete accord with the experimental facts and represent the human counterpart of the animal experiments of Goldblatt. As would be expected, the kidney with the markedly narrowed arterial orifice and lumen failed to show arteriolonecrotic changes, because there existed no hypertension within its vascular tree.

Thus, the relation of cause to effect in this patient is clear. The disease can be traced to the original trauma, which had caused partial thrombosis of the left renal artery. This in turn may be implicated in the gradually developing arterial hypertension. From the foregoing description it is also clear why the patient had the unilateral malignant nephrosclerosis with uremia from which he died.

Case 2 also clearly fulfils Goldblatt's prerequisite for certain instances of hypertension. The patient, a 35 year old woman, having suffered from severe arterial hypertension, died in uremia. Postmortem examination revealed a unilateral pyelonephritic contracted kidney (right) with associated severe obliterative arteriosclerotic changes in the arcuate and interlobar arteries and arteriolosclerosis. Further, one of the anomalous three right main arteries had a frankly constricted lumen. It is evident that the intrarenal arterial changes were produced by the old pyelonephritis which had led to contraction of this kidney. The changes in the renal arterial tree resulted in an ischemic kidney capable of precipitating a hypertensive state. In the presence of the markedly elevated arterial pressure, the arteriolar channels of the left (contralateral) kidney and of other organs and structures eventually showed sclerotic changes. The patient apparently got along quite well in spite of her high blood pressure until early ascending pyelonephritis of the contralateral kidney developed. In view of the severely damaged right kidney, the recent ascending pyelonephritis (left) sufficed to cause excretory renal insufficiency. As in the first case, the two factors essential for the development of unilateral renal arteriolonecrosis were present, namely, arterial hypertension within the vascular system of only one kidney and renal insufficiency. The differences in the 2 cases lie in the agents causing the narrowing of the renal arteries with resulting hypertension and the renal insufficiency. The clinical course and the essential pathologic changes were identical, and both patients died in uremia, just as patients do who present the classic clinical picture of what is called malignant hypertension and who at autopsy show malignant nephrosclerosis.

The intestinal tract of this patient presented grossly the picture of uremic enterocolitis. In experiments on the dog in which, as has been mentioned, constriction of both renal arteries is made severe or in which one renal artery is clamped and the ureter of the other kidney is ligated, there is often found a severe hemorrhagic type of enterocolitis. This is the result of arteriolonecrotic changes of the vessels in the submucosa. In our case such changes in the vessels of the intestinal tract, therefore, were expected. On histologic examination, however, few such changes were noted. The enterocolitis was then considered to be of uremic origin.

Since Goldblatt's original experiments there have appeared in the literature reports, notably those by Leiter,[4] Freeman and Hartley [5] and Pincoffs and Bradley,[6] of clearcut examples of constriction of the renal arteries by arteriosclerotic plaques or tumors, with consequent permanent arterial hypertension. The human equivalent, however, of experimentally produced unilateral malignant nephrosclerosis has not, to our knowledge, been recorded. In their study of chronic pyelonephritis, Weiss and Parker [7] vaguely alluded to unilateral malignant nephrosclerosis, but their pathologic criteria for this condition are unlike the accepted criteria. Very recently, Blackman [8] reported the occurrence of arteriolonecrotic changes in cases in which hypertension and renal insufficiency coexisted and noted a correlation between these findings and the patency of the main renal arteries. He did not, however, mention the occurrence of such unilateral lesions.

As far as we are able to determine, the occurrence of unilateral malignant nephrosclerosis is an extremely rare finding. It is possible, of course, that if more attention were paid at postmortem examination to the state of both renal arteries and to their mouths and if Goldblatt's experimental results were kept in mind such instances as are reported here would be found more frequently. As it is, perhaps, not so much the stark anatomic findings but his ability to explain the clinical findings in the light of his postmortem observations which intrigues the pathologist, it seems quite likely that more such instances as are recorded here will be made known as soon as the worker in this field is able to interpret the anatomic findings in the light of the history and the course of disease.

The third case is similar to those reported by Butler,[9] Leadbetter and Burkland,[10] McIntyre,[11] and Weiss and Parker.[7] The patient had

4. Leiter, L.: Unusual Hypertensive Renal Disease: 1. Occlusion of Renal Arteries (Goldblatt Hypertension); 2. Anomalies of Urinary Tract, J. A. M. A. **111**:507 (Aug. 6) 1938.

5. Freeman, G., and Hartley, G., Jr.: Hypertension in a Patient with a Solitary Ischemic Kidney, J. A. M. A. **111**:1159 (Sept. 24) 1938.

6. Pincoffs, M. C., and Bradley, J. E.: The Association of Adenosarcoma of Kidney (Wilms' Tumor) with Arterial Hypertension, Tr. A. Am. Physicians **52**:320, 1937.

7. Weiss, S., and Parker, F., Jr.: Pyelonephritis: Its Relation to Vascular Lesions and to Arterial Hypertension, Medicine **18**:221, 1939.

8. Blackman, S. S., Jr.: Arteriosclerosis and Partial Obstruction of the Main Renal Arteries in Association with "Essential" Hypertension in Man, Bull. Johns Hopkins Hosp. **65**:353, 1939.

9. Butler, A. M.: Chronic Pyelonephritis and Arterial Hypertension, J. Clin. Investigation **16**:889, 1937.

10. Leadbetter, W. F., and Burkland, C. E.: Hypertension in Unilateral Renal Disease, J. Urol. **39**:611, 1938.

11. McIntyre, D. W.: Unilateral Chronic Pyelonephritis with Arterial Hypertension: Apparent Cure After Nephrectomy, J. Urol. **41**:900, 1939.

a unilateral pyelonephritic and arteriosclerotic contracted kidney. The renal artery of this side was markedly constricted by a calcified plaque. The opposite kidney showed moderate arteriolosclerosis on microscopic examination but otherwise was practically normal. The patient had had severe arterial hypertension, which probably was the result of the changes in the renal artery and in the intrarenal arteries. The case is included in this series principally for comparison with cases 1 and 2. All 3 patients showed, clinically, arterial hypertension which was the result of constricting lesions in the arterial system of one kidney. The opposite kidneys in cases 1 and 2 showed anatomically the picture of malignant nephrosclerosis (arteriolonecrosis). In the light of the foregoing interpretation this may be easily understood. The question arises now as to why the contralateral kidney of the patient in case 3 did not show arteriolonecrosis. As previously stated, evidence was presented to show that there existed in the patients in cases 1 and 2 excretory renal insufficiency, an essential component for the production of the arteriolonecrosis. It is also noteworthy that these patients died in uremia. It seems evident that the patient in the third case did not live long enough to have excretory renal insufficiency. He died, not in uremia but as a result of bronchopneumonia.

The mechanism for the production of hypertension after constriction of the renal arteries is not known. However, it is apparent that ischemia of the kidney is the essential and constant feature of the phenomenon. Though poorly irrigated with blood, the kidney must contain sufficient functioning tissue if hypertension is to ensue. It is possible that the functioning tissue within the ischemic kidneys elaborates a pressor substance or that the pressor-regulating substances present in the normal kidney are destroyed in the ischemic kidney. Just what is present (or perhaps absent) in an ischemic kidney which is responsible for arterial hypertension is not known.

The question has been raised repeatedly whether Goldblatt's experimental findings are indeed applicable to human pathology and whether they explain the pathogenesis of so-called essential hypertension. As far as these 3 cases are concerned, there can be no doubt that the arterial changes, the counterpart of the clamping of the renal arteries in the experimental animals, were the etiologic factor. Particularly in the first case, in which a thrombus in the renal artery was found, there was, so to speak, an exact imitation by nature of Goldblatt's experiments. Thus, correlation of these experiments with actual human pathology and hypertension in man seems to be definite. In every instance of death from so-called essential hypertension, when arterial or arteriolar nephrosclerosis is not observed at autopsy, it is, therefore, imperative to search for a constricting lesion either at the mouth of the renal artery or within the main renal artery. Yet the most common

lesion found at postmortem examination in instances of so-called essential hypertension is arteriolosclerosis of both kidneys (nephrosclerosis of the arteriolar variety). In other words, the equivalent of the clamping of the main renal artery in the experimental dog seems to occur rarely in the human being, but the physiologic equivalent, renal ischemia, is brought about by obliterative sclerosis of the smallest branches, the arterioles. As Goldblatt [8] has stressed, the arteriolosclerosis of the kidneys corresponds to a million or more minute clamps in each kidney, the corollary of the single clamp around the main renal artery. However, the cause of arteriolosclerosis, which is the apparent cause of so-called essential hypertension, still remains conjectural.

Human beings, in contradistinction to dogs and rabbits, are capable of experiencing a long-standing arterial hypertension after obliterative vascular disease has involved only one kidney. One other experimental animal, the rat, reacts fairly consistently to unilateral renal vascular stenosis, sustained hypertension developing in 65 per cent (Wilson and Byrom [12]). The fact that hypertension may develop in human beings after unilateral renal vascular stenosis brings to realization a very practical point of importance. It means that the internist, when confronted by a patient with persistent arterial hypertension, should keep in mind the possibility that the hypertension may be secondary to renal changes. When this primary and causative disturbance is unilateral and when the effects of the established hypertension on the vascular tree of the rest of the body, particularly the opposite kidney, are still nil or minimal, removal of the unilaterally ischemic kidney may be curative. There are in the literature descriptions of patients with unilateral pyelonephritis and arterial hypertension whom nephrectomy cured of the hypertension (Butler; [9] Leadbetter and Burkland; [10] McIntyre; [11] Boyd and Lewis, [13] and others). However, it must be especially remembered that nephrectomy for these patients should be considered only in instances of unilateral disease in which the opposite kidney is still free of arteriosclerotic and arteriolosclerotic changes. Failure to adhere strictly to this tenet will result in grave injustice to the patient, for unwarranted removal of the kidney will not cure the hypertension but will immediately make the patient a candidate for the development of fatal uremia incident to the progression of the already present disease process in the one remaining kidney. Such failure of nephrectomy is not a condemnation of the procedure but rather a condemnation of the lack of judgment of the attending internist and surgeon, or of the inability by present methods to detect vascular

12. Wilson, C., and Byrom, F. B.: Renal Changes in Malignant Nephrosclerosis: Experimental Evidence, Lancet **1**:136, 1939.

13. Boyd, C. H., and Lewis, L. G.: Nephrectomy for Arterial Hypertension, J. Urol. **39**:627, 1938.

disease in the other kidney. Nephrectomy is a perfectly logical and warranted procedure in the very carefully selected case. The difficulty in all these instances lies in recognition of the cause of the hypertension and in evaluation of the state of the opposite kidney. If the arterial hypertension is caused by bilateral nephrosclerosis of the arteriolar variety, nothing can be done to cure the patient. If it is caused by changes in one renal artery or in its intrarenal branches (unilateral pyelonephritis), a timely nephrectomy may cure the patient. It will not be difficult for the physician to rule out or to diagnose unilateral pyelonephritis. In time it may also be possible to diagnose unilateral ischemic kidney as the result of a lesion at the mouth of the renal artery or within the main renal artery itself. Selection of patients for operation must depend on intelligent correlation of the tests of renal function (done separately on each kidney), pyelographic studies and evaluation of the vascular system as determined by the status of its accessible parts (retinal, coronary and peripheral vessels). For the 3 patients described in this communication, nephrectomy at the time of hospitalization, even if possible, would have been unwarranted and harmful, for by that time changes had already taken place in the contralateral kidney and other vessels. Much earlier removal of the ischemic kidneys, however, would probably have cured these patients.

SUMMARY

Three cases of severe arterial hypertension secondary to unilateral renal vascular stenosis with consequent ischemia of one kidney are reported. In 2 of these autopsy revealed unilateral malignant nephrosclerosis (arteriolonecrosis). Because of recent experimental evidence, this unique observation could be readily explained. From his experimental studies, primarily concerned with the production of arterial hypertension by clamping the renal arteries in the dog, Goldblatt concluded that both hypertension and renal insufficiency are the minimal prerequisites for the induction of arteriolonecrosis, for in the absence of either of these factors no necrotizing changes are observed. The patients in both these cases had severe arterial hypertension brought about by renal artery changes with resulting ischemia of one kidney. Both subsequently had renal excretory insufficiency. This was precipitated in 1 instance by the onset of congestive heart failure and in the other by the development of acute ascending pyelonephritis in the kidney opposite the ischemic one. Because of the presence of the severe arterial hypertension and excretory renal insufficiency, the arterioles in the contralateral kidneys (with a patent vascular system) showed necrotic changes, and these kidneys presented the typical picture of malignant nephrosclerosis. The arterioles in the ischemic kidneys revealed no necrotic changes because the stenosis of the renal and

intrarenal arteries militated against the presence of severe hypertension within the arterioles. Thus, the pathogenesis of the malignant nephrosclerosis in these cases is exactly similar to that of the arteriolonecrotic changes produced experimentally by Goldblatt. The third case was included in this report for comparative purposes. This patient died of intercurrent bronchopneumonia and never showed evidences of renal insufficiency. In this instance the requisite factors for development of the malignant phase of hypertension were lacking and, as was expected, there was no evidence of arteriolonecrosis on postmortem examination.

Dr. J. Gutman and W. Buchbinder permitted use of the clinical record in case 1; Dr. N. Crohn, use of that in case 2, and Dr. R. Herzog, use of that in case 3.

PULMONARY INFECTION AND NECROSIS IN DIABETES MELLITUS

REPORT OF A CASE OF DISSECTING NECROTIC PNEUMONIA COMPLICATING PANCREATIC LITHIASIS

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The true nature of the lowered resistance to infection associated with diabetes mellitus is poorly understood despite a wealth of clinical and experimental information. Earlier writers [1] favored the view that it depended on hyperglycemia and saturation of the tissues with dextrose, since many micro-organisms, including diphtheroids, molds and cocci, had been shown to grow by preference in mediums containing sugar. More recent experiments, by Richardson,[2] Marble and his associates,[3] Pillsbury and Kulchar [4] and others, on the contrary, indicate that increased sugar content of blood and tissues is not significant in bringing about increased growth of bacteria in the body or in diminishing the resistance of the host. Although experimental staphylococcic cutaneous ulcers in dogs undergo rapid necrosis after large intraperitoneal injections of dextrose, this occurs only with solutions sufficiently hypertonic to have toxic effects, and these results can also be duplicated with hypertonic sodium chloride solution.[4]

The humoral mechanism of immunity in diabetic patients has been reported in older studies [5] to be defective when measured in terms of

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From the Laboratory and Medical Service of St. Peter's Hospital, New Brunswick, N. J.

1. (*a*) Naunyn, B.: Der Diabetes Mellitus, in Nothnagel, H.: Specielle Pathologie und Therapie, Vienna, A. Hölder, 1900, vol. 7, p. 170. (*b*) Lassar, O.: Ernährungstherapie bei Hautkrankheiten, Dermat. Ztschr. **11**:189, 1904.

2. Richardson, R.: (*a*) Immunity in Diabetes: I. Influence of Diabetes on the Development of Antibacterial Properties in the Blood, J. Clin. Investigation **12**:1143 (Nov.) 1933; (*b*) II. Relative Importance of Nutritional State and of Blood Sugar Level in Influencing Development of the Agglutinin After Typhoid Vaccine, ibid. **14**:389 (July) 1935.

3. Marble, A.; White, H. J., and Fernald, A. T.: The Nature of the Lowered Resistance to Infection in Diabetes Mellitus, J. Clin. Investigation **17**: 423 (July) 1938.

4. Pillsbury, D. M., and Kulchar, G. V.: The Relation of Experimental Skin Infection to Carbohydrate Metabolism: The Effect of Hypertonic Glucose and Sodium Chlorid Solutions Injected Intraperitoneally, Am. J. M. Sc. **190**: 169 (Aug.) 1935.

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serum complement, bacteriostasis, opsonic index and antibody response to injected antigens. According to more recent observations, however, serum complement [6] and bacteriostatic and bactericidal properties [5] have been shown to be undiminished. Antibody production after injections of vaccine may yield serum titers well within normal limits.[6a] The explanation of the reduced opsonic activity of diabetic blood has also been shown to lie in a lowered activity of diabetic leukocytes rather than in a fault in serum opsonins.[6a] The tendency has grown to attach only relative significance to humoral immune responses, since they are now regarded only as special phases or extensions of tissue immunity.[7]

Recent studies [8] strengthen the view that the lowered resistance to infection observed in persons with diabetes is primarily an aspect of faulty metabolism of the tissues. The evidence at present does not, however, localize the impaired resistance within the cellular elements the activity of which is specifically anti-infective, such as the reticuloendothelial system,[9] the lymphatic apparatus and the leukocytes. Instead, the fault apparently resides within all tissues of the body and concerns their intrinsic biologic capacity to withstand injury and intoxication of any kind, whether infectious, chemical or ischemic. Horster,[6a] for example, demonstrated greater inflammatory reaction and necrosis in skin of depancreatized dogs with diabetes than in nondiabetic controls. This could be accomplished with local injection of turpentine as well as with staphylococci. Shorr observed more rapid in vitro autolysis of

5. Moen, J. K., and Reimann, H. A.: Immune Reactions in Diabetes, Arch. Int. Med. **51**:789 (May) 1933. Richardson.[2a]

6. (*a*) Horster, H.: Untersuchungen über die durch Krankheiten hervorgerufene Änderung der Disposition für Infektion, bzw. für Erkrankung nach Infektion. Beitrag zur Klärung der Ursache der verminderten Widerstandsfähigkeit des zuckerkranken Organismus gegen Infektion, Deutsches Arch. f. klin. Med. **176**:502, 1934. (*b*) Richardson.[2a]

7. Kahn, R. L.: Tissue Immunity, Springfield, Ill., Charles C. Thomas, Publisher, 1936. Teale, F. H.: Some Observations on the Relative Importance of the Reticulo-Endothelial Tissues and the Circulating Antibody in Immunity: I. Bacterial Immunity in Relation to the Role Played by the Circulating Antibody and the Tissues Following Intravenous Introduction of the Bacteria, J. Immunol. **28**:133 (Feb.) 1935; II. Hypersensitiveness and Immunity to Foreign Proteins: An Analysis of the Parts Played by the Tissues and Circulating Antibody in These Two States, ibid. **28**:161 (March) 1935. Dienes, L.: The Specific Immunity Response and the Healing of Infectious Diseases, Arch. Path. **21**: 357 (March) 1936.

8. Bayne-Jones, S.: The Effects of Carbohydrates on Bacterial Growth and Development of Infection, Bull. New York Acad. Med. **12**:278 (May) 1936. Horster.[6a]

9. Harrington, H. L., and Huggins, C.: Rate of Removal of Thorium Dioxide from the Blood Stream, Arch. Int. Med. **63**:445 (March) 1939.

diabetic heart and skeletal muscle than control specimens [10a] and suggested that the defective oxidation of carbohydrate by diabetic tissue in vitro is possibly explained by an inhibitory factor of pituitary origin.[10b] Other possible contributory factors may be mentioned. The metabolism of vitamin A is thought to be defective in cases of diabetes,[11] as is that of vitamin C.[12] Both vitamins are concerned in the maintenance of tissue integrity against infection and other injury. The pattern of cell debility in cases of untreated diabetes bears many similarities to that of extreme undernutrition [13] and avitaminosis [14] as well as of the cachexias associated with advanced malignant disease, heart failure and senility.

The pernicious nature of infection in cases of diabetes is a matter of everyday experience to the clinician, not only in respect to the skin and the contiguous mucosae but in respect to the viscera, particularly the lungs. The threat of pulmonary tuberculosis has received recent emphasis by Fitz,[15] Root,[16] Steinbach and his associates,[17] McKean and Myers [18] and many other writers. Both "diabetic phthisis" and "diabetic nonputrid gangrene of the lung" with characteristic extensive necrosis of lung tissue are mentioned frequently in the older (preinsulin) literature of diabetes.[19] For the former are described enormous numbers

10. Shorr, E.: (*a*) Personal communication to the author; (*b*) Restoration of Carbohydrate Oxidation in Diabetic Tissue in Vitro, Science **85**:456 (May 7) 1937.

11. Ralli, E. P.; Pariente, A. C.; Brandaleone, H., and Davidson, S.: Effect of Carotene and Vitamin A on Patients with Diabetes Mellitus: III. Effect of Daily Administration of Carotene on Blood Carotene of Normal and Diabetic Individuals, J. A. M. A. **106**:1975 (June 6) 1936.

12. Pfleger, R., and Scholl, F.: Diabetes und Vitamin C, Wien. Arch. f. inn. Med. **31**:219, 1937.

13. Bieling, R.: Unterernährung und Infektion, Deutsche med. Wchnschr. **53**:228 (Feb. 4) 1927.

14. Clausen, S. W.: The Influence of Nutrition upon Resistance to Infection, Physiol. Rev. **14**:309 (July) 1934. Robertson, E. C.: The Vitamins and Resistance to Infection, Medicine **13**:123 (May) 1934.

15. Fitz, R.: The Problem of Pulmonary Tuberculosis in Patients with Diabetes, Am. J. M. Sc. **180**:192 (Aug.) 1930.

16. Root, H. F.: (*a*) Association of Diabetes and Tuberculosis, New England J. Med. **210**:1 (Jan. 4); 78 (Jan. 11); 127 (Jan. 18); 192 (Jan. 25) 1934; (*b*) Tuberculosis Complicating Diabetes, in Joslin, E. P.: The Treatment of Diabetes Mellitus, ed. 6, Philadelphia, Lea & Febiger, 1937, chap. 21, p. 496.

17. Steinbach, M. M.; Klein, S. J., and Deskowitz, M.: Experimental Diabetes and Tuberculosis in the Dog, Am. Rev. Tuberc. **32**:665 (Dec.) 1935.

18. McKean, R. M., and Myers, G. B.: Metabolic Aspect of Associated Diabetes Mellitus and Pulmonary Tuberculosis, Ann. Int. Med. **8**:1591 (June) 1935. Myers, G. B., and McKean, R. M.: Diabetes and Tuberculosis, Am. Rev. Tuberc. **32**:651 (Dec.) 1935.

19. (*a*) Kornrumpf, P.: Ueber Lungenkomplikationen bei Diabetes, Inaugural Dissertation, Berlin, E. Ebering, 1914. (*b*) Fink, H.: Beitrag zur Lehre von

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of tubercle bacilli; for the latter, a mixture of large numbers of molds, diphtheroids and other saprophytes. Tuberculosis in an untreated diabetic person may, under certain conditions, bring about rapid liquefying necrosis of almost an entire pulmonary lobe. At autopsy only a shell of thickened pleura remains, enclosing a giant cavity filled with sloughed tissues.[20] Proper treatment, however, promises the diabetic person with pulmonary tuberculosis a far more hopeful outlook.[21]

The predisposition of the inflamed lung in cases of untreated diabetes to undergo necrosis may be apparent even in the presence of common grippal bronchitis and bronchopneumonia [19a] and to an even more striking degree in cases of fungous infections [22] and of putrid abscess of the lung.[23] Although a low incidence of pneumococcic lobar pneumonia is recorded in association with diabetes,[24] cases of severe pulmonary infection have been described in which the early course resembled lobar pneumonia clinically but in which the outcome was atypical if not disastrous. This will be discussed later.

Especial attention should be given to the role played in pulmonary infection by deficiency of the pancreas when it is caused by chronic disease of the parenchyma with extensive atrophy. In such a case fatty diarrhea goes hand in hand with diabetes mellitus to bring about pronounced emaciation and physical debility. Despite the fact that diabetes is often mild, a high incidence of pulmonary infection is reported. Among the best known instances are those which occur in cases of congenital steatorrhea with fibrosis of the pancreas.[25] Death occurs usually in early childhood as a result of bronchopneumonia. Postmortem

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der diabetischen Lungenerkrankung, Inaug. Dissert., Giessen, C. von Münchow, 1887. (*c*) Marchand, F.: Ueber den Ausgang der Pneumonie in Induration, Virchows Arch. f. path. Anat. **82**:334, 1880. (*d*) Fraenkel, A.: Spezielle Pathologie und Therapie der Lungenkrankheiten, Berlin, Urban & Schwarzenberg, 1904. (*e*) Naunyn,[1a] pp. 218 and 220.

20. Moolten, S. E.: Unpublished data.

21. Wessler, H., and Hennell, H.: Benign Pulmonary Tuberculosis with Diabetes, Am. Rev. Tuberc. **27**:47 (Jan.) 1933. Root.[16b]

22. Fürbringer, P.: Beobachtungen über Lungenmycose beim Menschen, Virchows Arch. f. path. Anat. **66**:330, 1876. Wätjen, J.: Durch Schimmel-und Sprosspilze bedingte Erkrankungen der Lunge, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1931, vol. 3, pt. 3, p. 481.

23. Rabin, C. B.: Personal communication to the author.

24. Marble, A., in Joslin, E. P.: The Treatment of Diabetes Mellitus, ed. 6, Philadelphia, Lea & Febiger, 1937, chap. 14, p. 407. Root.[16b]

25. (*a*) Harper, M. H.: Congenital Steatorrhea Due to Pancreatic Defect, Arch. Dis. Childhood **13**:45 (March) 1938. (*b*) Parmelee, A. H.: The Pathology of Steatorrhea, Am. J. Dis. Child. **50**:1418 (Dec.) 1935. (*c*) Andersen, D. H.: Cystic Fibrosis of the Pancreas and Its Relation to Celiac Disease, ibid. **56**: 344 (Aug.) 1938.

examination reveals subacute bronchopneumonia with purulent bronchitis, widely disseminated miliary abscesses and bronchiectases. Since steatorrhea is often associated with deficient absorption of fat-soluble vitamins, these pulmonary lesions have been attributed to changes brought about by vitamin A deficiency.[26] In Andersen's series of 49 cases, keratinizing metaplasia of the bronchial epithelium was frequently noted.[25c] In this connection it is important to recall the fact that xerophthalmia occurs only in extreme cases of vitamin A deficiency in the human being, while fairly early in the course of the deficiency the ciliated epithelium of the respiratory tract may disappear.[27]

Severe pancreatic deficiency of long duration in the adult is best exemplified in pancreatic lithiasis. The literature of this condition is rich in instances of its association with pulmonary tuberculosis of great destructiveness.[28] The high incidence of this association led, in fact, to the erroneous supposition of early observers that the pancreatic lesion is a result of tuberculosis.[28b]

Aside from tuberculosis, no well defined type of pulmonary disease has been described in any of the reported cases of pancreatic calculus except one. This was a case published in the Dutch literature by Peutz [29] in 1930 under the descriptive title of "acute aputrid necrosis of the lung." The patient was a diabetic man aged 43. He had been treated for diabetes since the age of 25 and had recently become considerably emaciated. Four weeks before entering the hospital he had a productive cough and dyspnea and felt sudden severe pain in the right side of his chest. On admission he was cyanotic and intensely dyspneic and had physical signs suggestive of pneumothorax. The roentgenogram was reported to show encapsulated hydropneumothorax. Autopsy revealed large, irregular intrapulmonic cavities with a shaggy lining of recently softened lung tissue. They were filled with nonputrid liquid pus and air and occupied most of the right lung and a few areas of the left. One of the cavities in the lower lobe of the right lung was the size of a fist. The surrounding lung was consolidated and had patches of peculiar yellowish white necrosis which had not yet undergone softening. There were no evidences of tuberculosis grossly or microscopically. The pan-

26. Darrow, D. C., in discussion on Parmelee.[25b] Andersen.[25c]

27. Wolbach, S. B., and Howe, P. R.: Epithelial Repair in Recovery from Vitamin A Deficiency, J. Exper. Med. **57**:511 (March) 1933.

28. (*a*) Möckel, E.: Ueber Lithiasis pancreatica mit vier eigenen Fällen, Frankfurt. Ztschr. f. Path. **24**:78, 1921. (*b*) Gruber, G. B.: Speicheleindickung und Speichelsteine im Pankreas, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1929, vol. 5, pt. 2, p. 382. (*c*) Ackman, F. D., and Ross, A.: Pancreatic Lithiasis, Surg., Gynec. & Obst. **55**:90 (July) 1932.

29. Peutz, J. L. A.: Acute aputriede longnecrose bij pancreasdiabetes, Nederl. tijdschr. v. geneesk. **74**:3659 (July 19) 1930.

creas was almost entirely transformed into dense scar tissue and contained many small calculi.

A close counterpart of this case is seen in the following case.

REPORT OF CASE

J. J., a man aged 54, entered St. Peter's Hospital with "advanced pulmonary tuberculosis and diabetes mellitus." For five years he had been subject to attacks of agonizing cramplike pain in the epigastrium; at times the attacks persisted as long as five days despite repeated large doses of morphine. During the later months of his illness he had persistent diarrhea and began to lose weight rapidly. Diabetes was discovered and treated by diet without insulin. Three months before admission to the hospital he began to cough and expectorate frequently. On admission he was gravely ill and was emaciated to a striking degree. His feet were edematous. Marked dulness and numerous moist rales were detected over the entire right lung. His urine contained 5 per cent sugar but no acetone; the value for blood sugar was 333 mg. per hundred cubic centimeters. The level of hemoglobin was normal (85 per cent, Dare); there were 4,700,000 red blood cells and 7,250 white blood cells per cubic millimeter, with 80 per cent polymorphonuclear leukocytes. The temperature ranged between 97 and 99.4 F. He died thirty-six hours after admission.

Postmortem Examination.—The subject appeared extremely cachectic and emaciated. The right lung was heavy and largely consolidated. The upper lobe was partly adherent, and its visceral pleura was greatly thickened by fibrosis. On section the entire upper lobe exhibited grayish white consolidation with numerous large areas of partial or complete liquefaction necrosis. Many sequestrums of inflamed and necrotic lung tissue floated partly free in the cavities thus formed, and some of the parenchyma had become dissected away from the surrounding inflamed tissue as well as from the pleura and interlobular septums and bronchi. Fresh cavities had shaggy, friable walls; older ones were lined in part by smooth whitish material like pyogenic membrane. They contained grayish muddy fluid without distinctive odor. In certain portions of the consolidated areas small foci of tuberculosis were also seen, which were recognized by their dense fibrous scar tissue containing anthracotic pigment and both calcified and caseous deposits. The blood vessels showed no significant changes.

Microscopically many shreds of faintly stained necrotic parenchyma were seen. These were composed of the ghosts of alveolar septums containing necrotic exudate and ghosts of occasional bronchi and blood vessels (fig. 1). A wide zone of suppuration separated these necrotic areas from the remaining tissue and formed the lining of cavities (fig. 2). In some areas tissue necrosis had just begun, and only an indefinite line of demarcation had appeared at the edges. The intervening parenchyma exhibited exudation varying from edema and epithelial desquamation to massive infiltration with polymorphonuclear leukocytes and fibrin, especially in the vicinity of the most active necrosis. Patchy carnification was also noted. The bronchi and bronchioles in intact areas were distended with partly necrotic purulent exudate. The blood vessels in necrotic areas were completely destroyed. In the line of demarcation they exhibited inflammatory thromboses, the thin-walled veins being chiefly affected. There were no vascular lesions, either arterial or venous, in areas proximal to the demarcating inflammation.

The tuberculous foci were also affected by necrosis; in a few the envelope of scar tissue had been destroyed and the caseous contents partly liberated. Small

secondary patches of recent tuberculosis were noted in close proximity to the necrotic areas described and often merged insensibly into them. These exhibited caseation with very little formation of granulation tissue. Giant cells of the Langhans type were lacking.

Bacterial stains of the necrotic portions revealed enormous numbers of bacteria and bacterial colonies, chiefly gram-positive bacilli morphologically suggestive of Bacillus subtilis and very short gram-negative bacilli. Prolonged search

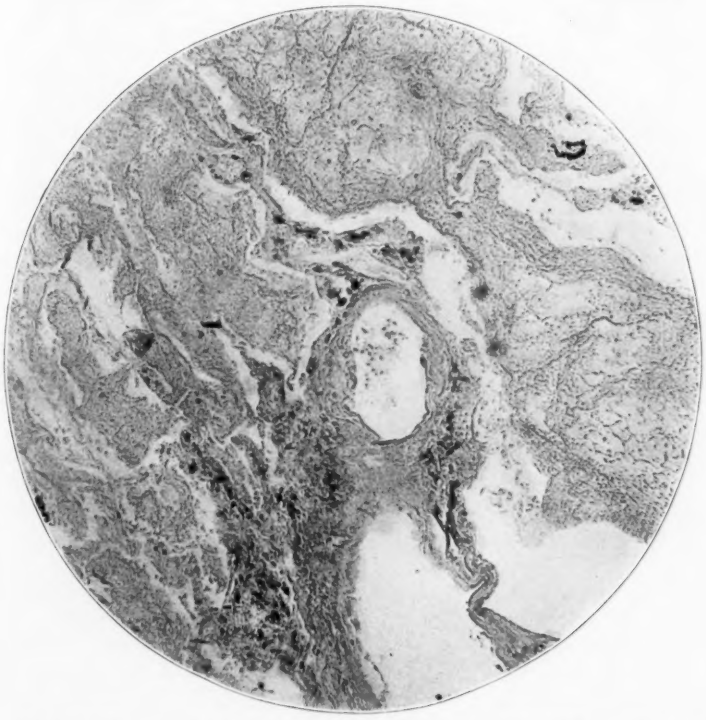

Fig. 1.—Sequestrum of the lung; alveolar and bronchial "ghosts" containing faintly stained exudate of fibrin and leukocytes are seen.

yielded no evidence of yeasts, molds or encapsulated bacilli or cocci. Tubercle bacilli were not seen in these necrotic areas. A few were discovered in the tuberculous foci just described.

The lower lobe of the right lung was markedly congested and presented a few small scattered areas of recent caseous tuberculosis. These presented almost no granulation tissue reaction but contained many tubercle bacilli. The left lung showed only congestion and some emphysema.

The pancreas was of average size (fig. 3) but exceedingly hard and buried in adhesions. It was cut with great difficulty and seemed to be completely transformed into fibrous tissue of almost woody consistency. Within it were embedded

many white calcareous particles. The main pancreatic duct (Wirsung's) was greatly dilated throughout its length. A white calculus 4 by 4 by 7 mm. was firmly impacted in its lumen, about 1 cm. above its duodenal orifice. Several

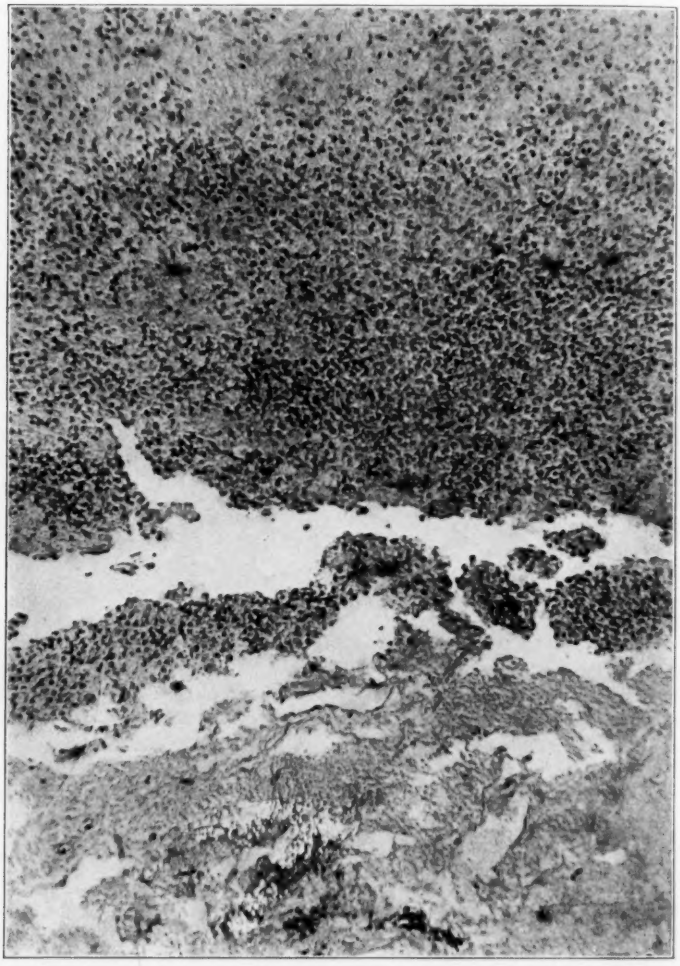

Fig. 2.—Wall of the cavity, showing the pyogenic membrane and separation of a sequestrum of necrotic lung tissue.

smaller, irregular, gritty white calculi lay free in the lumen behind this. Microscopically all but a few scattered nests of gland tissue had become replaced by dense hyaline scar. Within these remnants the acini were loosely disposed; in some areas they were fairly well preserved and elsewhere they were atrophic (fig. 4).

The collecting ducts were dilated and filled with epithelial debris, a few leukocytes and rounded laminated masses resembling corpora amylacea. The islets of Langerhans were few and somewhat atrophic, with small round pyknotic nuclei.

Both kidneys were studded with innumerable tiny furuncular lesions which projected slightly on the surface and on cut section extended toward the medulla as tapering whitish streaks. Microscopically they appeared as minute abscesses containing a mixture of bacteria morphologically similar to those seen in the sections of the necroses within the lung. Diffuse infiltration of polymorphonuclear leukocytes extended irregularly through the remainder of the interstitia.

The colon was moderately distended with pasty, unformed brownish gray feces. When held to the light the feces had a conspicuous silvery sheen, as though there were a high fat content. The odor was distinctively rancid.

The myocardium, liver and kidneys presented parenchymal degeneration, such as is seen in acute infection. Microscopically the liver cells were somewhat shrunken and were devoid of fat vacuoles; occasional nuclei contained glycogen vacuoles. The portal fields showed moderate infiltration of lymphocytes and increase in fibrous tissue. The myocardial fibers stained unevenly, often with hydropic replacement of fibrillae or vacuoles and with much bipolar yellow pigment.

The spleen presented the changes of severe infection. Both adrenals were enlarged considerably by rounded, bulging acorn-sized tumors composed of yellowish tissue; histologically they were composed of hyperplastic cortex containing abundant lipoid and presenting a few areas of recent focal degeneration.

Clinical Diagnosis.—The clinical diagnosis was diabetes mellitus without ketosis.

Anatomic Diagnoses.—The anatomic diagnoses were as follows: multiple calculi of the pancreatic duct, with atrophy and fibrosis of the entire pancreas; steatorrhea; extreme emaciation and cachexia; anasarca; massive necrotic pneumonia of the upper lobe of the right lung, with multiple cavities (pneumonia dissecans necrotica); slight localized recent tuberculosis of the upper and lower lobes of the right lung, secondary to decapsulation of old fibrocaseous tuberculous foci of the upper lobe; conglomerate miliary hematogenous ("excretion") abscesses of both kidneys with acute interstitial nephritis, and adenomatous hyperplasia of the cortex of the adrenal glands with focal degeneration.

Comment.—Excellent discussions of pancreatic calculus are available in the writings of Gruber,[28b] Gross,[30] Mayo Robson and Cammidge,[31] Barron[32] and Crohn.[33] Attacks of severe epigastric pain, prolonged fatty diarrhea, diabetes mellitus and extreme emaciation constitute a fairly typical clinical syndrome, permitting easy recognition in the advanced stages of the disease. Diagnosis before the development of

30. Gross, O.: Konkremente im Pankreas, in Gross, O., and Guleke, H.: Die Erkrankungen des Pankreas, Enzyklopaedie der klinischen Medizin, Spezieller Teil 5 c, Berlin, Julius Springer, 1924, p. 206.

31. Mayo Robson, A. W., and Cammidge, P. J.: The Pancreas: Its Surgery and Pathology, Philadelphia, W. B. Saunders Company, 1907.

32. Barron, M.: The Relation of the Islets of Langerhans to Diabetes with Special Reference to Cases of Pancreatic Lithiasis, Surg., Gynec. & Obst. **31**: 437 (Nov.) 1920.

33. Crohn, B. B.: Disturbances of Metabolism Accompanying Pancreatic Disease, in Barker, L. F., and others: Endocrinology and Metabolism, New York, D. Appleton and Company, 1922, vol. 4, p. 657.

irreversible pancreatic insufficiency, however, is much more difficult without roentgen examination. Fortunately, practically all pancreatic stones are radiopaque and thus permit early diagnosis and the possibility of surgical cure.[34]

NECROSIS OF THE LUNG AND NECROTIC PNEUMONIAS

Interest in the present case centers principally on the pulmonary lesion, the outstanding feature of which was necrosis. While necrosis in general is not uncommon in a variety of pulmonary diseases, its significance is almost always bound up with the nature of the underlying

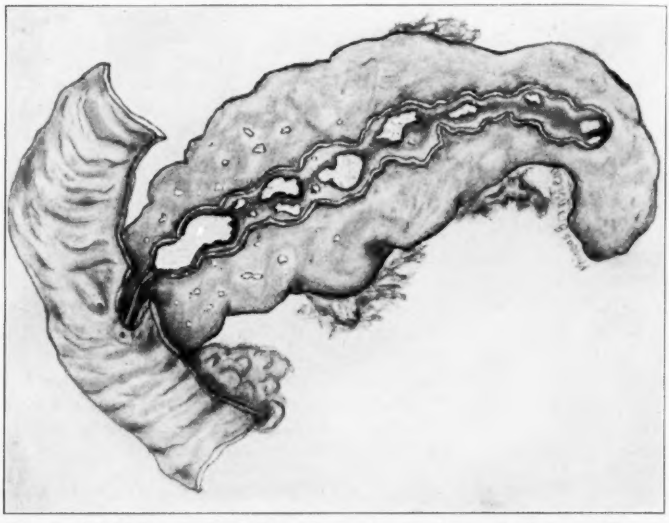

Fig. 3.—Multiple calculi of the main pancreatic duct and of the smaller ducts. Note the marked fibrosis of the entire gland and the separate opening of the pancreatic duct into the duodenum 1 cm. from the papilla of Vater.

infection. Minute areas of necrosis are fairly common in ordinary bronchopneumonia but are not detectable clinically. They are apparent at autopsy as small grayish white areas within larger patches of severe inflammation.[35] This may be marked in influenzal bronchopneumonia.[35b] In the earliest stages of necrosis the affected tissue is slightly firmer than normal, suggesting a process of coagulation, and owes its grayish white color to bloodlessness brought about by injury to its capillaries. The framework of elastic tissue is often well preserved, as is proved by

34. Lindsay, E. C.: A Further Case of Multiple Pancreatic Calculi: Removal and Recovery, Lancet **1**:700 (April 7) 1928. Bost, T. C.: Pancreatic Lithiasis:

histologic methods, but the other elements of the parenchyma, as well as the cellular and fibrinous exudates, stain poorly or not at all. When softening occurs, fragments of necrotic parenchyma may still be recognized as "ghosts" within areas of suppuration.

It has been suggested [36] that such foci of necrosis within the parenchyma of the lung are the basic factor in the formation of the common saccular bronchiectases. According to this theory, as air is sucked into

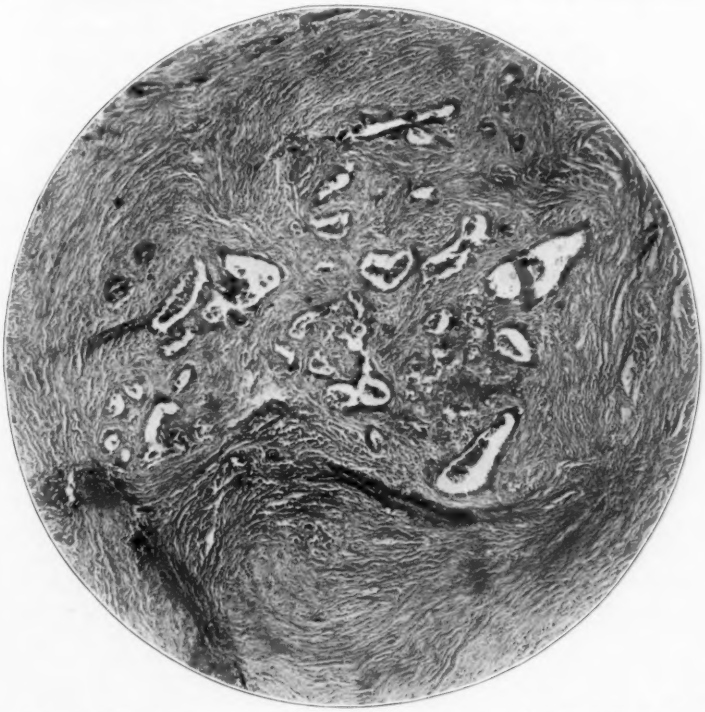

Fig. 4.—Fibrosis of the pancreas. Scattered remnants of dilated acini and ducts embedded within dense scar tissue are seen.

Report of Cases, Am. J. Surg. **29**:85 (July) 1935. Haggard, W. D., and Kirtley, J. A., Jr.: Pancreatic Calculi: Review of Sixty-Five Operative and One Hundred and Thirty-Nine Nonoperative Cases, Ann. Surg. **109**:809 (May) 1939.

35. (*a*) Hartwell, J. A., and Dudley, G. S.: Abscess of the Lung, in Nelson's New Loose-Leaf Medicine, New York, Thomas Nelson & Sons, 1927, vol. 3, p. 503. (*b*) MacNalty, A. S., and Malloch, A.: Influenza, ibid., vol. 1, p. 608.

36. Moolten, S. E.: Mechanical Production of Cavities in Isolated Lungs, Arch. Path. **19**:825 (June) 1935.

the lungs by breathing, it enters these areas of tissue breakdown after purulent softening has taken place and expands them into rounded cavities many times their original size. Their expanded, rounded form is made permanent by subsequent fibrosis of their walls. An epithelial lining derived from the nearest draining bronchi replaces part of the pyogenic membrane, and, as a result, the sacculi often seem to resemble direct outgrowths of these bronchi instead of by-products of destruction of the lung tissue itself. Larger cavities, arising in areas of more extensive necrosis, are explained by the same mechanism. The ultimate size of such cavities is generally far greater than the original defect in the lung and is governed by the pressure of inspiration and of cough and by the degree of yielding of the surrounding fibroelastic framework.

Small patchy foci of necrotic softening occur not infrequently in lobar pneumonia,[37] particularly in infection with type III pneumococci [37d] and the Friedländer bacillus,[38] and probably result from primary toxic injury by these organisms.[37a] Somewhat less often a large circumscribed area of necrosis is encountered, which is apparently the result of ischemia from vascular thrombosis ("aputrid anemic necrosis").[39] Clinically, this lesion is discovered accidentally in the course of roentgen examination during convalescence from pneumonia, as it rarely produces clinical symptoms by itself. Its benign course and ultimate healing were first pointed out to me by Dr. H. Wessler [40] and were made the subject of an excellent publication by Kessel.[41]

Infection by putrefactive anaerobic organisms pursues a distinctive course,[42] typified in the familiar "putrid lung abscess." This is virtually

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37. (*a*) Reinisch, M.: Zur Entstehung der Pneumonienekrose, Virchows Arch. f. path. Anat. **290**:75 (Aug.) 1933. (*b*) Letulle, M.: Anatomie pathologique, Paris, Masson & Cie, 1931, vol. 1, p. 690. (*c*) Lauche, A.: Die Entzündungen der Lunge und des Brustfelles, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1928, vol. 3, pt. 1, p. 758. (*d*) Finland, M.; Brown, J. W., and Ruegsegger, M.: Anatomic and Bacteriologic Findings in Infections with Specific Types of Pneumococci, Including Types I to XXXII, Arch. Path. **23**:801 (June) 1937. Finland, M., and Sutliff, W. D.: Infections with Pneumococcus Type III and Type VIII, Arch. Int. Med. **53**:481 (April) 1934. (*e*) Hartwell and Dudley.[35a]

38. Bullowa, J. G. M.; Chess, J., and Friedman, N. B.: Pneumonia Due to Bacillus Friedländeri: A Report on Forty-One Patients with Consideration of Specific Serum Therapy, Arch. Int. Med. **60**:735 (Nov.) 1937. Solomon, S.: Primary Friedländer Pneumonia, J. A. M. A. **108**:937 (March 20) 1937. Sweany, H. C.; Stadnichenko, A., and Henrichsen, K. J.: Multiple Pulmonary Abscesses Simulating Tuberculosis, Caused by the Friedländer Bacillus, Arch. Int. Med. **47**:565 (April) 1931.

39. Rosenthal, T.: Ueber den Ausgang der fibrinösen Pneumonie in aputride anämische Nekrose, Inaug. Dissert., Berlin, G. Schade, 1907. Lauche.[37c]

40. Wessler, H.: Personal communication to the author, 1928.

41. Kessel, L.: The Clinical Aspects of Aputrid Pulmonary Necrosis, Arch. Int. Med. **45**:401 (March) 1930.

a form of carbuncle with a central core of putrid necrosis. In its primary phase it is generally a solitary lesion. Rarely it presents itself as diffuse putrid gangrene of the lung. The principal distinguishing feature of putrid infection is its odor.

When infection is caused by a fungus or by one of the higher bacteria, destruction of lung tissue may be progressive and very extensive. Common examples are seen in infection with actinomyces,[43] the streptothrix [44] and, in weakened persons, the aspergillus.[45]

In the face of such a miscellany of causes of necrosis it is quite impossible to set it up as a landmark of classification in itself. However, when the occurrence of necrosis signifies something beyond its purely bacterial causation, such as a faulty degree of resistance by the host's tissues, it is useful to include it in the designation of the infection. The term necrotic pneumonia should be employed descriptively provided the bacterial cause, when known, is prefixed or implied; e. g., in streptothrix necrotic bronchopneumonia.[44c]

Taken as a group, necrotic pneumonias may defy differentiation from tuberculosis of the lung in their roentgen and clinical features. Tests of the sputum are usually diagnostic, and tuberculous caseation is easily distinguished at autopsy from the necrosis of other infections. One exception to this should be noted. In severely cachectic persons with terminal hyperacute tuberculosis, the caseous material may be much softer and more liquefied than ordinarily, and smears may reveal enormous numbers of tubercle bacilli. In such an instance the specific histologic features of tuberculous granulation tissue are lacking.[46] In conformity with morphologic classification, the condition in these cases should be termed "tuberculous necrotic bronchopneumonia."

Necrosis in the presence of inflammation may be stated generally to depend on two factors, the destructiveness of the bacterial agent and the destructibility of the host's tissue. The former is of concern here only in so far as it defines the specific character of the infection. The latter

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42. Neuhof, H., and Wessler, H.: Putrid Lung Abscess, J. Thoracic Surg. **1**:637 (Aug.) 1932. Touroff, A. S. W., and Moolten, S. E.: The Symptomatology of Putrid Abscess of the Lung, J. Thoracic Surg. **4**:558 (Aug.) 1935.

43. Arndt, H. J.: Die aktinomykotischen Veränderungen der Lunge und des Brustfells und das Verhalten der Lunge und des Brustfells bei Aktinomykose, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1931, vol. 3, pt. 3, p. 397.

44. (*a*) Arndt, H. J.: Die Streptotrichose der Lunge und des Brustfells, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1931, vol. 3, pt. 3, p. 459. (*b*) Moolten, S. E.: Streptotrichotic Suppuration of the Lung Following Aspiration of a Foreign Body, J. Mt. Sinai Hosp. **1**:147 (Nov.-Dec.) 1934. (*c*) Page, I. H.: Streptothrix Necrotic Bronchopneumonia, Arch. Int. Med. **41**:127 (Jan.) 1928.

45. Moolten, S. E.: A Case of Primary Broncho-Pulmonary Aspergillosis, J. Mt. Sinai Hosp. **5**:29 (May-June) 1938. Footnote 22.

46. Moolten, S. E.: Unpublished data.

is the chief factor which governs the outcome in the individual case. Constitutional factors deserve particular attention in all considerations pointing to this end, both when necrosis is characteristic of the infection and when it is not. The relation of diabetes to the development or aggravation of necrosis has already been discussed. The theory of that relation is based on cellular suboxidation leading to loss of vital potencies. Other forms of pronounced debility predispose to the same result, whether due to senility, undernutrition, uremia or extensive malignant disease.

ACUTE SUPPURATIVE BRONCHOPNEUMONIA

Neuhof and others [47] have recently directed attention to certain forms of bronchopneumonia complicated by an unusual degree of suppuration. Because of their apparently increased incidence and tendency to abscess formation they have been grouped together as a clinical entity under the title "acute suppurative bronchopneumonia." These are encountered as a complication of grip, purulent sinusitis, whooping cough, measles or bronchial obstruction. They may follow contamination of the bronchi by aspirated secretions or vomitus. Within the inflamed lobe or lobes multiple areas of softening occur. These form cavities of the order of saccular bronchiectases or larger or coalesce to form enormous solitary cavities which simulate pyopneumothorax in the roentgen film. Expectoration is copious, but the sputum is not foul. Empyema and pyopneumothorax may follow and may require surgical drainage. A fatal outcome is not uncommon, although in some cases the lesions undergo unexpected spontaneous disappearance, with complete recovery.

Complete pathologic study has been possible in a limited number of cases. From the descriptions given it appears that in certain instances the lesion is undoubtedly a form of necrotic bronchopneumonia like that complicating influenza. In cases of this sort, suppuration follows in the wake of necrosis. A variety of aerobic organisms has been found, including pneumococci, streptococci, staphylococci and the Friedländer bacillus, as well as certain anaerobic diphtheroids and streptococci. It is not clear at present how many of these are to be regarded as secondary invaders. In other instances it is possible that the lesion should be classified as a form of hyperacute interstitial bronchopneumonia in which suppuration is part of phlegmonous inflammation and probably caused by hemolytic streptococci.

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47. (*a*) Neuhof, H., and others: Complications and Sequelae of Suppurative Bronchopneumonia, J. Mt. Sinai Hosp. **3**:36 (May-June) 1936. (*b*) Neuhof, H., and Touroff, A. S. W.: Acute Aerobic (Nonputrid) Abscess of the Lung, Surgery **4**:728 (Nov.) 1938. (*c*) Sussman, M. L.: Non-Putrid Pulmonary Suppuration, Am. J. Roentgenol. **40**:22 (July) 1938. (*d*) Rabin, C. B.: Radiology of the Chest, in Golden, R.: Diagnostic Roentgenology, New York, Thomas Nelson & Sons, 1936.

Data concerned with constitutional factors of resistance (e. g., diabetes) are not yet available.

INTERSTITIAL AND DISSECTING PNEUMONIAS

An important feature of infections of the lung by hemolytic streptococci is their tendency to localize within the interstitial framework. Accordingly, the term interstitial pneumonia has been applied when the predominant inflammation lies within this framework, which includes the peribronchial and perivascular sheaths, the subpleural connective tissue and the interlobular and interlobar septums with their finer intralobar subdivisions.[48]

Dissecting pneumonia, as the term implies, is pulmonary inflammation in which portions of the lung become detached or "dissected" from supporting tissues. The affected tissue is broken up into small or large fragments which lie within cavities filled with blood and pus.[49]

The usual form of dissecting pneumonia occurs as a complication of acute interstitial pneumonia in which suppuration spreading into the lung from the pleura along interlobular and subpleural septums brings about the separation of fairly large blocks of parenchyma. This is often accompanied by suppurative mediastinitis and suppurative pleuritis with empyema. In this type, seen most often in childhood, cavities are produced which contain sequestrums of all or most of the substance of the inflamed lobe. Such sequestrums become softened and may be discharged piecemeal into the empyema cavity or may be coughed up. Interstitial suppuration may proceed along the peribronchial sheaths to produce a similar result.

DISSECTING NECROTIC PNEUMONIA

The term "dissecting necrotic pneumonia" was applied in 1921 by Letulle and Bezançon [50] to a lesion similar to that observed in the present case. The extent of the lesion over an entire lobe, the dissecting type of necrosis, the absence of foul odor, the mixed bacterial flora and the clinical findings set this type of necrotic pneumonia apart from "putrid lung abscess" or gangrene and from various other specific infections, such as the mycoses. The extent of tissue destruction is far greater and far less circumscribed than that of the "aputrid necrosis," or small patchy necrotic areas, already mentioned, which may complicate ordinary lobar pneumonias. Its closest counterpart is seen in certain of the cases reported as examples of "acute suppurative bronchopneumonia" in which the destructive process involves nearly an entire lobe, with production of an enormous nonputrid abscess.[47b]

48. Lauche,[37c] p. 835.

49. (*a*) Letulle,[37b] p. 687. (*b*) André, L.: La pneumonie disséquante, Thesis, Paris, no. 294, Paris, Jouve & Cie, 1920. (*c*) Lauche.[48]

50. Letulle, M., and Bezançon, F.: La pneumonie disséquante nécrotique, Ann. de méd. **12**:1 (July) 1922.

The clinical picture or dissecting necrotic pneumonia was more or less consistent in the 4 cases described by Letulle and Bezançon. The onset was marked by sudden chill, high fever, pain in the chest, severe dyspnea and intense toxemia. Despite these evidences of pneumonia, early physical signs were meager and for the most part consisted in scattered coarse rales and harsh breath sounds. At first the sputum was mucopurulent and moderate in amount. After ten to twenty days the patient was seized with violent cough and quickly emptied his lungs of an enormous quantity of bloody purulent liquid of reddish brown or chocolate color. From then on the sputum remained hemorrhagic and had a stale, musty or garlic-like odor, but it was not foul. Signs of cavitation were then obtained, and roentgenograms showed an enormous vomica with a broad fluid level which could be mistaken for hydropneumothorax because of its size. In all 4 cases the condition was fatal.

Necropsy studies of these cases appeared to indicate that the underlying process was coagulative necrosis occurring in already consolidated lung. This was succeeded by a stage of intense leukocytic infiltration and digestion followed by liquefaction and cavity formation. Various stages coexisted side by side. The cavities were irregular and were lined with shaggy sloughs and fragments of lung tissue. These had become detached in whole or in part from more resistant structures, such as the bronchi and septums, and produced the appearance of massive sequestration, or "dissection." The distribution of the necroses did not follow anatomically predetermined patterns, however, as in the interstitial forms of dissecting pneumonia or the necroses caused by vascular closure. With the spread of the process the cavities enlarged and coalesced until almost the entire lobe was converted into one huge cavity containing brownish fluid and sloughing sequestrums of tissue. A minor degree of carnification occurred in the edges of the lesion, and the overlying pleura became greatly thickened and adherent. Blood vessels overtaken by the advance of the lesion were destroyed or thrombosed.

So far as causation is concerned, the striking feature of the disease was the luxuriant growth of a variegated mixed flora without predominant type. Pneumococci were not observed regularly, and other organisms, such as the Friedländer bacillus and various streptococci, were regarded as incidental contaminants. Among other things, the authors stressed the great importance of physical debility as an etiologic factor. Three of their patients were persons past middle age, and the fourth, a man aged 24, had chronic tuberculosis and diabetes mellitus. In a fifth case, reported later by Roubier and others,[51] the condition occurred

51. Roubier, C.; Froment, R., and Planchu, M.: Vaste cavité purulente intrapulmonaire occupant la totalité du lobe supérieur gauche, chez un diabétique, Lyon méd. **147**:313 (March 8) 1931.

in a diabetic patient aged 67. Peutz's [29] case of pancreatic calculus, which has been described, apparently falls into the same category. Two cases reported by Neuhof and Touroff [47b] (cases 9 and 10) are probably also instances of this type.

On the basis of its morphologic features it would seem desirable to include the condition in the present case among the foregoing ones. As is noted in the autopsy protocol, the entire upper lobe of the right lung was in part consolidated and in part necrotic. Large masses of lung tissue had become sequestrated, forming irregular sloughs within cavities. These were filled with nonodorous fluid and swarmed with a mixture of micro-organisms which resembled the saprophytic flora of decaying tissue.

The unusually high incidence of pulmonary tuberculosis in cases of pancreatic calculus has already been mentioned. In the present case tuberculosis was an inconspicuous part of the final picture, but seemed to have been reactivated to a limited degree by the necrotic pneumonia. The latter may possibly have owed its localization within the upper lobe of the right lung to preexistent latent tuberculosis, and it is possible, too, that latent tuberculosis played a part in reducing the general vitality of the patient.

"DIABETIC NONPUTRID GANGRENE OF THE LUNG"

The development of the modern treatment of diabetes mellitus has altered considerably the relative incidence of its principal factors of morbidity and mortality. Whereas infection formerly stood in the first rank, its position has been largely superseded by complications of much slower development, especially arteriosclerosis.

This change is nowhere better reflected than in the limited emphasis now placed on the pulmonary complications of diabetes, as contrasted with that shown in older treatises. While pulmonary tuberculosis still occupies a major position, little mention is now made of other varieties of diabetic pneumopathy, especially that referred to as "diabetic gangrene of the lung." Naunyn,[19c] Fraenkel [19d] and others [19a] described a condition not unlike dissecting necrotic pneumonia under this heading. In its onset it resembled severe lobar pneumonia with hemorrhagic sputum which was almost never foul and with fatal termination in a few weeks. Multiple foci of necrosis were seen in the lung at autopsy, usually with one of large size. These areas were brownish red or grayish white, odorless and either softened or suppurating. The surrounding tissue was consolidated. Mixed bacterial growth was observed, as well as yeasts. A peculiar softening of the lung was also described by several authors,[52]

52. Kaufmann, E.: Lehrbuch der speziellen pathologischen Anatomie, ed. 7-8, Berlin, W. de Gruyter & Co., 1922, vol. 2, p. 319. Beitzke, H.: Atmungsorgane, in Aschoff, L.: Pathologische Anatomie, ed. 6, Jena, Gustav Fischer, 1923, vol. 2, p. 279. Rosenthal.[39]

under the title of "diabetic pneumomalacia." Infection and vascular occlusions apparently played little or no primary part. This lesion was described as aputrid necrosis of pale color and "tinder-wood" appearance, often honeycombed with cavities and usually confined to small circumscribed areas but at times comprising a considerable extent of brownish red rotting tissue without odor. Superinfection with saprophytic organisms from the upper air passages occurred frequently. Fraenkel [19d] suggested that nonputrid gangrene of the lung is a special form of diabetic pneumomalacia.

In the last analysis the various forms of nonputrid "diabetic gangrene of the lung" can be resolved into one or another of the categories of necrotic pneumonia of nonspecific (mixed) bacterial causation. It is a needless refinement of classification to individualize them on the basis of diabetes, since, as has been indicated, untreated diabetes is only one of many factors of lowered tissue resistance by which these necrotic pneumonias are linked. Dissecting necrotic pneumonia, while morphologically distinctive, cannot be separated etiologically on any basis but one of degree. Similarly, the mixed flora swarming in the sloughs of this lesion are to be regarded as opportunistic invaders of secondary virulence or as saprophytes, such as are seen in any decaying tissue.

SUMMARY

The impaired resistance to infection in diabetic persons is probably part of a general vulnerability of diabetic tissues to injury of any type and is related to deficient cellular oxidation. Both cellular repair and immunity responses may be seriously affected.

The unfavorable prognosis of pulmonary tuberculosis in cases of poorly treated diabetes is well known. Other pulmonary infections may also prove disastrous, particularly those which invite suppuration and necrosis. Of peculiar interest is the predisposition of patients with prolonged pancreatic insufficiency to pulmonary suppuration and pulmonary tuberculosis. The former is frequent in cases of congenital steatorrhea associated with fibrosis of the pancreas; the latter, in cases of pancreatic lithiasis.

A case of pancreatic lithiasis is described in which chronic pancreatic insufficiency with diabetes mellitus was complicated by extensive necrotic pneumonia of mixed bacterial type. Only 1 similar case has been reported in the literature. This type of pneumonia appears to be identical with that described by Letulle and Bezançon under the heading of "dissecting necrotic pneumonia" and differs from other forms of necrotic and suppurative pneumonia in its distinctive morphologic and clinical features. As in the present case, it is probably to be regarded as a special instance of the particular disposition of cachetic tissues to undergo necrosis.

STRUCTURAL CHANGES IN THE ARTERIOLES OF THE MYOCARDIUM IN DIFFUSE ARTERIOLAR DISEASE WITH HYPERTENSION GROUP 4*

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That diffuse arteriolar changes occur in the presence of essential hypertension seems well established. However, controversy exists concerning the exact nature, distribution, frequency of occurrence and severity of these changes.

Numerous investigators (Keith, Wagener and Kernohan;[1] Cain;[2] Moritz and Oldt;[3] Fishberg;[4] Pilcher and Schwab;[5] Morlock,[6] and others) have studied the changes occurring in the arterioles of selected organs in cases of hypertension. It has been reported by some investigators (Fishberg; Pilcher and Schwab) that when hypertension is present the changes noted in the arterioles of other organs almost never are observed in the arterioles of the myocardium.

LITERATURE

The first suggestion as to the occurrence of vascular change in association with hypertension was embodied in the observation of Bright[7]

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* Some objection has been raised to the use of the term "malignant hypertension." In the following report, the terms "diffuse arteriolar disease with hypertension group 4" and "malignant hypertension" have been used interchangeably.

Abridgment of a thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Medicine. (Work done in the Section on Pathologic Anatomy.)

1. Keith, N. M.; Wagener, H. P., and Kernohan, J. W.: The Syndrome of Malignant Hypertension, Arch. Int. Med. **41**:141-188 (Feb.) 1928.

2. Cain, E. F.: Malignant Hypertension: The Histologic Changes in the Kidneys, Arch. Int. Med. **53**:832-850 (June) 1934.

3. Moritz, A. R., and Oldt, M. R.: Arteriolar Sclerosis in Hypertensive and Non-Hypertensive Individuals, Am. J. Path. **13**:679-728 (Sept.) 1937.

4. Fishberg, A. M.: Anatomic Findings in Essential Hypertension, Arch. Int. Med. **35**:650-668 (May) 1925.

5. Pilcher, J. F., and Schwab, E. H.: Arteriolar Changes in Essential Hypertension, Texas State J. Med. **28**:665-668 (Feb.) 1933.

6. Morlock, C. G.: Arterioles of the Pancreas, Liver, Gastro-Intestinal Tract and Spleen in Hypertension, Arch. Int. Med. **63**:100-118 (Jan.) 1939.

7. Bright, R.: Cases and Observations, Illustrative of Renal Diseases Accompanied with the Secretion of Albuminous Urine, Guy's Hosp. Rep. **1**:338-400, 1836.

in 1836 that certain patients who had chronic Bright's disease also had noticeable thickening of the blood vessels.

Johnson,[8] in 1850, observed thickening of the arteriolar walls of the kidney in the presence of chronic Bright's disease, and he [9] later demonstrated the existence of similar changes in the arteriolar walls of skin, skeletal muscle, intestine and pia mater.

Johnson expressed the belief that this thickening is caused by hypertrophy of the muscular elements of the tunica media, and he concluded that arteriolar spasm is an important factor. Primary renal degeneration, in his opinion, leads to retention of urinary constituents in the blood, and, because the peripheral arterioles resist the flow of impure blood, the heart is called on to beat against an increased peripheral resistance. This process, he reasoned, results in simultaneous hypertrophy of the arteriolar walls and of the left ventricle of the heart.

Four years later, Gull and Sutton [10] confirmed Johnson's observations but expressed the opinion that arteriolar thickening is caused not by hypertrophy of the medial musculature but by a hyaline fibroid degenerative change to which they applied the term "arterio-capillary fibrosis," a change which could be demonstrated in the kidney, brain, retina, spleen and skin. Gull and Sutton [10] concluded that contraction and atrophy in the kidney referable to vascular changes are only part of a generalized vascular change and that, although the changes commonly originate in the kidney, they may also be primary in other organs.

Mahomed [11] observed that an elevated blood pressure may exist for some time in the absence of any signs of damage to the kidneys. He labeled this phase "the pre-albuminuric stage of chronic Bright's disease," but in reality he had discovered essential hypertension. He concluded that hypertension and the subsequent cardiovascular changes are the primary condition and that renal symptoms are secondary. Mahomed stated that certain cases occur in which the cardiovascular changes associated with Bright's disease are present but in which no marked changes can be discovered in the kidneys.

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8. Johnson, G.: On the Proximate Cause of Albuminous Urine and Dropsy, and on the Pathology of the Renal Blood-Vessels in Bright's Disease, Tr. Roy. Med.-Chir. Soc. London **33**:107-120, 1850.

9. Johnson, G.: I. On Certain Points in the Anatomy and Pathology of Bright's Disease of the Kidney; II. On the Influence of the Minute Blood-Vessels upon the Circulation, Tr. Roy. Med.-Chir. Soc. London **51**:57-76, 1868.

10. Gull, W. W., and Sutton, H. G.: On the Pathology of the Morbid State Commonly Called Chronic Bright's Disease with Contracted Kidney, Tr. Roy. Med.-Chir. Soc. London **55**:273-326, 1872.

11. Mahomed, F. A.: The Etiology of Bright's Disease and the Prealbuminuric Stage, Tr. Roy. Med.-Chir. Soc. London **57**:197-228, 1874; Some of the Clinical Aspects of Chronic Bright's Disease, Guy's Hosp. Rep. **24**:363-436, 1879.

Ewald's [12] observations, made in 1877, confirmed the presence of medial hypertrophy as described by Johnson. Ewald particularly stressed thickened arteriolar walls and narrowed lumens, and he emphasized that the increase in thickness of the wall is caused by a simple increase in the number of muscle fibers.

Jores [13] observed hyaline and fatty changes in the intima and hyperplasia of the internal elastic lamina in the visceral arterioles of hypertensive patients. These changes, he found, had led to a narrowing of the lumens of the arterioles and had occurred most frequently in the arterioles of the kidney, brain, spleen, pancreas and intestine. Jores was unable to demonstrate any change in the arterioles of skeletal muscle.

He concluded that when a diffuse arteriolar lesion is present it is degenerative and is limited to the intima. He strongly denied the existence of muscular hypertrophy; instead, he emphasized the process as one of arteriosclerosis. Like Gull and Sutton, Jores expressed the opinion that the vascular changes are widespread, sometimes leading to renal disease and at other times to cardiac or cerebral failure with normal renal function.

In 1914, Volhard and Fahr [14] postulated the existence of a toxic factor which, when superimposed on the arteriosclerotic changes associated with benign hypertension, produces the malignant form of the disease. Volhard [15] later repudiated the theory that the vascular and glomerular changes found in the presence of malignant hypertension are inflammatory, and he expressed the belief that the lesions are the result of ischemia brought about by prolonged vascular spasm.

Fahr [16] likewise revised his ideas on the subject and expressed his later conviction that benign hypertension is the result of simple arteriosclerosis of the larger arterioles and malignant hypertension the result of inflammatory and necrotic arteriolar changes on a toxic basis. He

12. Ewald, C. A.: Ueber die Veränderungen kleiner Gefässe bei Morbus Brightii und die darauf bezüglichen Theorien, Virchows Arch. f. path. Anat. **71**:453-499 (Dec.) 1877.

13. Jores, L.: Ueber die arteriosklerose der kleinen Organarterien und ihre Beziehungen zur Nephritis, Virchows Arch. f. path. Anat. **178**:367-406, 1904; Ueber den pathologischen Umbau von Organen (Metallaxie) und seine Bedeutung für die Auffassung chronischer Krankheiten insbesondere der chronischen Nierenleiden (Nephrozirrhosen) und der Arteriosklerose; nebst Bemerkungen über die Namengebung in der Pathologie, ibid. **221**:14-38, 1916.

14. Volhard, F., and Fahr, K. T.: Die Brightsche Nierenkrankheit; Klinik, Pathologie und Atlas, Berlin, Julius Springer, 1914.

15. Volhard, F.: Der arterielle Hochdruck, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **35**:134-175, 1923.

16. Fahr, T.: Ueber Nephrosklerose, Virchows Arch. f. path. Anat. **226**:119-178, 1919; Ueber die Beziehungen von Arteriolensklerose, Hypertonie und Herzhypertrophie, ibid. **239**:41-63, 1922.

minimized the inflammatory nature of the glomerular lesions and emphasized the inflammatory vascular lesions, which he chose to designate as "necrotizing arteriolitis."

Allbutt,[17] in 1915, stated that in his opinion hypertension may exist for years without the appearance of any signs of renal damage and that death may eventually occur as the result of cerebral or cardiac failure. He expressed the belief that "hyperpiesia" is caused by a dynamic factor rather than by an organic narrowing of the peripheral arterioles but that elevation of the blood pressure over a long period may result in generalized arteriolar thickening.

Wagener and Keith,[18] in 1924, reported a series of 14 cases of marked hypertension, severe retinitis and adequate renal function. In all cases death occurred within forty-four months after the onset of symptoms. Because of this, Wagener and Keith proposed the term "malignant hypertension" for the condition.

Fishberg expressed the belief that the earliest pathologic change occurring in essential hypertension is the deposition in the afferent arterioles of the kidney of hyalin, which later undergoes fatty change. In larger vessels a hyperplastic intimal thickening takes place, with subsequent hyalinization and proliferation of surrounding connective tissue, which leads to narrowing and possibly to complete obliteration of the lumen. The tunica media, Fishberg said, shows little or no change until late in the process, when it undergoes atrophy and fibrosis. In his opinion, the renal arterioles are involved more frequently than are those of any other organ. He observed changes in the arterioles of the myocardium in only 2 of 68 cases studied, and he was unable to demonstrate structural changes in the arterioles of skeletal muscle.

Keith, Wagener and Kernohan,[19] in 1928, reported 81 cases of malignant hypertension. It was of interest to the authors that many patients died as a result not of failure of one vital organ but of simultaneous failure of several organs; for example, of cerebral, cardiac and renal failure. Seven patients came to necropsy, and the arteriolar changes were noted. Microscopically, the arterioles exhibited marked hyperplasia of the intima and hypertrophy of the tunica media and internal elastic lamina. Perivascular fibrosis was present in varying degrees. There were almost no signs of degenerative change.

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17. Allbutt, T. C.: Diseases of the Arteries Including Angina Pectoris, London, Macmillan Company, Ltd., 1915, vol. 1, pp. 378-454.

18. Wagener, H. P., and Keith, N. M.: Cases of Marked Hypertension, Adequate Renal Function and Neuroretinitis, Arch. Int. Med. **34**:374-387 (Sept.) 1924.

19. Keith, N. M.: Classification of Hypertension and Clinical Differentiation of the Malignant Type, Am. Heart J. **2**:597-608 (Aug.) 1927. Keith, Wagener and Kernohan.[1]

The investigators stressed especially the diffuse and widespread involvement of all organs by the process, the medial hypertrophy and the intimal thickening, and they expressed the opinion that the thickening, if steadily progressive, ultimately would lead to occlusion of the lumen of the arteriole. In their opinion, this fact supports Volhard's ischemic theory and offers a logical explanation for the diffuse parenchymatous lesions associated with this syndrome.

Like Fishberg, Bell and Clawson [20] expressed the opinion that marked hyperplastic intimal thickening of the afferent glomerular arteries is almost conclusive evidence of the presence of hypertension and that this thickening rarely occurs in the absence of hypertension.

In 1929, Kernohan, Anderson and Keith [21] made a histologic study of the changes in the arterioles of specimens of pectoral muscle taken for biopsy from 53 patients who had hypertension, the hypertension of 11 patients being benign, that of 18 patients severe benign (or early malignant) and that of 23 patients malignant. The condition of the 1 remaining patient, who had chronic glomerulonephritis, was studied for comparison with the condition of other patients, who had diffuse arteriolar disease with hypertension. Material for controls was obtained from pectoral muscles of patients without hypertension and at necropsy from patients without elevated blood pressure or cardiac enlargement. The mean normal wall to lumen ratio was found to be 1:2, with variations from 1:1.7 to 1:2.7. In cases of benign hypertension the mean ratio was 1:1.4, with variations from 1:1.1 to 1:1.8. In cases of severe benign and malignant hypertension the mean ratio was 1:1.1, with variations from 1:0.9 to 1:1.7. There was slight increase in the perivascular connective tissue. The most pronounced and most usual change was hypertrophy of the tunica media with an increase in the nuclear elements. They noted no medial fibrosis and almost no evidence of degenerative change. There were hyperplasia and, in some cases, splitting of the internal elastic lamina. The intimal changes were varied, but the most constant finding was proliferation of the endothelial and subendothelial cells, sometimes to such a degree that the lumen was almost completely occluded.

In 1931, Klemperer and Otani [22] analyzed 16 cases of malignant nephrosclerosis and concluded that the primary lesion was arteriosclerosis of the small renal vessels. They stated that there were two

20. Bell, E. T., and Clawson, B. J.: Primary (Essential) Hypertension: A Study of Four Hundred and Twenty Cases, Arch. Path. **5**:939-1002 (June) 1928.

21. Kernohan, J. W.; Anderson, E. W., and Keith, N. M.: The Arterioles in Cases of Hypertension, Arch. Int. Med. **44**:395-423 (Sept.) 1929.

22. Klemperer, P., and Otani, S.: "Malignant Nephrosclerosis" (Fahr), Arch. Path. **11**:60-117 (Jan.) 1931.

distinct types, one of which was a slowly progressive form of sclerosis producing a gradual constriction of the vascular bed with destruction of renal parenchyma and the other a rapidly developing vascular change with which there was no marked atrophy of the kidneys.

Keith, Barker and Kernohan [23] in 1931 made a histologic study of the arterioles of pectoral muscle of 143 patients suffering from hypertensive disease. Their group 1 included 11 patients who had chronic glomerulonephritis with hypertension. Arteriolar changes as described by Kernohan, Anderson and Keith were found to affect 4 of the 11 patients (36 per cent). Groups 2, 3, 4 and 5 corresponded to groups 1, 2, 3 and 4, respectively, as described by Keith, Wagener and Kernohan. Keith, Barker and Kernohan concluded from their observations that the anatomic changes in the arterioles in the presence of hypertensive disease occur more often among patients with severe hypertension but that the changes are not in proportion to the duration or elevation of the blood pressure.

Scott, Seecof and Hill, [24] in 1933, demonstrated that the appearance of specimens of skeletal muscle obtained for biopsy from hypertensive patients was practically the same as that of specimens from the same patients when eventually they came to necropsy and that the intensity of the arteriolar lesions in the kidney agreed closely with that observed in the specimens of skeletal muscle at both biopsy and necropsy.

Pilcher and Schwab studied the arteriolar changes in various organs of 15 patients with hypertension and observed a significant decrease in the wall to lumen ratios for all organs except the myocardium. They could not explain the absence of changes in the myocardial arterioles but suggested as a possible explanation that the demand for increased blood supply by the hypertrophied heart might have resulted in the formation of new blood vessels.

Cain, in 1933, made a study of the pathologic changes in the renal arterioles of 27 patients with malignant hypertension, and he observed an apparent increase in the number of endothelial cells in each instance, with subendothelial, fatty and hyaline degeneration, an apparent thickening of the media and an increase in perivascular connective tissue. The wall to lumen ratios of the renal arterioles were reduced to less than 1 : 1.0 in all but a single instance.

Moritz and Oldt have concluded from their study of the arteriolar changes associated with hypertension that intimal hyalinization, medial

23. Keith, N. M.; Barker, N. W., and Kernohan, J. W.: Histologic Studies of the Arterioles in Various Types of Hypertension, Tr. A. Am. Physicians **46**:66-70, 1931.

24. Scott, R. W.; Seecof, D. P., and Hill, A. A.: Anteriolar Lesions of Skeletal Muscle in Hypertension, Tr. A. Am. Physicians **48**:283-288, 1933.

hypertrophy and degeneration and intimal proliferation are the three principal changes characterizing the disease. Lesser degrees of thickening are felt to be the result of medial hyperplasia, whereas more advanced thickening is the result of degeneration and thickening of the tunica media and intima. Moritz and Oldt concluded that these changes occur in direct proportion to the size of the arteriole and that the decrease in the wall to lumen ratio is caused not by narrowing of the lumen but by increased thickness of the wall. The difference in this ratio between the hypertensive and the nonhypertensive group was not sufficient in 80 per cent of the cases to permit distinction, but in more than 80 per cent of the cases the hypertensive and the nonhypertensive patients could be classified as such by the presence or absence of changes in the arteriolar walls. Moritz and Oldt also emphasized the segmental distribution of the pathologic changes in the arterioles of skeletal muscle.

Morlock has made a study of the arteriolar changes occurring in the liver, pancreas, intestinal tract and spleen of a series of patients with hypertension. He observed significant arteriolar changes in all the organs he studied. On the basis of pathologic change, he has shown the degree of thickening to be as pronounced in one organ as it is in another. He has demonstrated clearly that the degree of thickening and the amount of structural change in various arterioles increase with the severity of the disease and that the least degree of change occurs in the presence of benign hypertension, whereas the most profound changes are seen when the malignant form is present.

Recently, Rosenberg [25] has completed a study of vascular changes in the brain in the presence of severe hypertension and has shown that in patients with malignant hypertension the cerebral arterioles undergo luminal narrowing and that thickening and structural changes of the walls take place, similar to the changes described as occurring in other organs.

CLINICAL OBSERVATIONS

Forty-eight patients having diffuse arteriolar disease with hypertension group 4, or so-called malignant hypertension, were studied clinically. Thirty-three of the 48 patients were males, and 15 were females. The ages ranged from 7 to 75 years, the average being 43.5 years, but the majority of patients were between the ages of 40 and 60 years. The number of patients in each decade is given in table 1.

The duration of known hypertension varied from one month to ten years, with an average of two years and four months. Eight patients did not know they had hypertension until it was discovered on physical examination.

25. Rosenberg, E. F.: Personal communication to the author.

Three patients had a history of chronic glomerulonephritis which had been diagnosed five, six and seven years, respectively, prior to the onset of symptoms of malignant hypertension.

A survey of family histories revealed cerebral accident in 20 cases, cardiac failure or coronary occlusion in 12 and renal disease in 4. Six patients had living relatives with hypertension. The family history was irrelevant in 11 cases and unknown in 6.

The patients were placed in four groups, "cardiac," "renal," "cerebral" and miscellaneous, according to the predominant symptoms and observations. Abstracts of 3 illustrative cases are presented.

REPORT OF CASES

CASE 4.—A man 49 years of age registered at the Mayo Clinic on Nov. 13, 1924, complaining of dyspnea on exertion and orthopnea of two months' duration,

TABLE 1.—*Distribution of Ages by Decades: Forty-Eight Patients Having Diffuse Arteriolar Disease with Hypertension Group 4*

Decade	Patients	Per Cent
0- 9	1	2.1
10-19	0	0
20-29	6	12.5
30-39	9	18.7
40-49	17	35.4
50-59	12	25.0
60-69	2	4.2
70-79	1	2.1
Total	48	100.0

accompanied by persistent productive cough. For the same length of time he had been extremely nervous and restless. He had lost 15 pounds (6.8 Kg.). For two weeks he had been troubled with edema of the extremities, nausea, vomiting, substernal pain on inspiration, blurring of vision and vertigo. The patient's maternal grandfather had died after a cerebral accident.

On examination the patient's weight was 114 pounds (51.7 Kg.), and he appeared acutely ill. There was a definite uriniferous odor to his breath. Peripheral vascular sclerosis was present and was graded 2. To percussion, the heart measured 4 by 14 cm., and both a systolic and a diastolic murmur were heard at the apex. The aortic second sound was accentuated. The patient was orthopneic and had cyanosis grade 2. Moist rales were heard over the bases of both lungs. The edge of the liver was palpable 6 cm. below the right costal margin. There was massive edema of the sacral region, genitalia and extremities. Examination of the fundi disclosed severe retinitis with bilateral papilledema.

The patient's condition became progressively worse, and a pericardial friction rub developed on the thirteenth day in the hospital. On the same day he lapsed into coma. He died two days later.

CASE 13.—A farmer 48 years of age registered at the clinic on March 10, 1928, complaining of nocturia, frequency of urination and severe headaches of two and a half years' duration. At the onset, the patient had had a transient attack of

aphasia which had followed a severe headache. For six months he had noticed palpitation, dyspnea on exertion, orthopnea, precordial pain and frequent epistaxis. His father and a brother had died after cerebral accidents; his mother had died of congestive heart failure, and one brother had died of chronic glomerulonephritis.

On examination the patient weighed 159 pounds (about 72 Kg.). Peripheral vascular sclerosis was present and was graded 2 to 3. The heart measured 2.5 by 11.5 cm. The aortic second sound was accentuated (grade 2); there were a basal systolic murmur and a questionable apical systolic murmur. The patient had severe retinitis with bilateral edema of the optic disks.

He returned on May 13, complaining of nausea and vomiting, marked dyspnea on exertion, orthopnea, precordial pain, hemoptysis, oliguria, vertigo and blurred vision of two weeks' duration. He had definite orthopnea and cyanosis. His peripheral vascular sclerosis was graded 4. The heart measured 2 by 13 cm. Both the aortic and the pulmonic sounds were accentuated, the pulmonic second sound being louder than the aortic second sound. The first sound was roughened, and there was a basal diastolic murmur. There were moist rales in the bases of both lungs. The retinal observations were unchanged.

The patient became progressively worse, and Cheyne-Stokes respiration developed; pericarditis, anuria, mental confusion and muscular twitchings occurred. He lapsed into coma and died on the eleventh day.

Case 34.—A grocer 52 years of age registered at the clinic in March 1932. He was found in the street in a comatose state, with cyanosis, vomiting and right hemiparesis. He had had three convulsions. On regaining consciousness he stated that he had had occasional episodes of blurred vision, "pressure in the head" and substernal oppression for four years.

On examination peripheral sclerosis was present and was graded 2 to 3; it was of the rubbery type. There was an apical systolic murmur, but otherwise the results of examination of the heart were negative. Examination of the ocular fundi revealed severe retinitis with hemorrhages, cotton wool exudates and edema of the optic disks.

The patient returned on five different occasions between March 1932 and April 1933, each time complaining of vertigo, tinnitus, headaches, failing vision, weakness and dyspnea on exertion. He had had several attacks of unconsciousness in the past year, varying in duration from one to twelve hours.

The patient returned in August 1933, at which time his peripheral sclerosis was graded 3. The heart was markedly enlarged to the left; the rhythm was grossly irregular, and a loud, blowing systolic murmur could be heard over all areas. Results of examination of the ocular fundi were the same as on previous admissions. On October 6 the patient had a sudden attack of weakness and dizziness and lapsed into coma. His respirations became stertorous; cyanosis developed; two tonic convulsions occurred, and the patient died.

In 20 cases the predominant symptoms were cerebral; in 21, cardiac; in 3, renal, and in 4, referable to the gastrointestinal tract. In 24 cases the earliest symptoms were cerebral; in 15, cardiac, and in 6, renal.

The most common symptoms were headaches occurring in the early morning, visual disturbances, dyspnea and tachycardia. Urinary symptoms were relatively infrequent. Loss of weight and strength were important features in the majority of cases.

TABLE 2.—*Laboratory Data on Forty-Eight Patients Having Diffuse Arteriolar Disease with Hypertension Group 4*

Case	Sex	Age	Blood Pressure, Mm. of Mercury: Maximum Systolic	Maximum Diastolic	Minimum Systolic	Minimum Diastolic	Urine: Specific Gravity	Albumin, Grade	Erythrocytes, Grade	Blood: Hemoglobin *	Erythrocytes, Millions per Cu. Mm. of Blood	Leukocytes per Cu. Mm. of Blood	Urea, Mg. per 100 Cc. of Blood	Creatinine, Mg. per 100 Cc. of Blood	Sulfates, Mg. per 100 Cc. of Serum	Chlorides, Mg. per 100 Cc. of Plasma	Plasma Carbon Dioxide-Combining Power, Vols. per 100 Cc. of Blood
1	F	45	255	150	200	140	1.026	1	0	82%	5.11	13,000	34	1.9	....	...	..
2	F	55	260	160	210	130	1.018	3	0	79%	4.00	10,400	33	1.8	....	...	..
			...	...	...	...	.....	..	..	76%	....	.....	134	7.4	....	...	..
3	F	42	240	140	222	130	.....	..	..	76%	....	.....	63	2.6	....	...	..
4	M	49	220	140	184	90	1.013	trace	0	56%	3.36	19,200	355	19.0	....	...	..
5	M	46	238	155	170	90	1.023	3	0	67%	3.52	5,000	48	2.1	....	558	53
			...	...	...	...	.....	..	..	61%	....	13,600	115	4.1	....	...	..
6	M	65	240	140	188	108	1.018	1	0	87%	4.62	19,000	101	4.5	....	642	53
7	F	46	294	176	170	96	1.015	4	occ	64%	3.30	24,400	204	8.8	....	...	..
8	M	40	220	169	168	128	1.015	4	0	72%	4.00	16,200	518	17.0	....	....	52
			...	...	...	...	.....	..	..	....	....	.....	...	....	....	530	23
9	M	50	260	170	180	90	1.020	2	1	58%	3.17	32,400	158	7.1	....	640	55
10	M	40	255	130	230	110	1.012	1	0	40%	2.56	8,200	242	10.4	....	...	..
11	M	39	230	150	165	96	1.015	2	0	65%	3.48	10,900	382	9.6	....	...	..
			...	...	...	...	.....	..	..	....	....	.....	...	....	....	...	18
12	M	23	250	174	148	92	1.020	4	1	80%	4.96	11,800	40	....	....	528	68
			...	...	...	...	.....	..	..	....	....	15,200	54	....	....	...	..
13	M	48	220	167	160	110	1.020	3	occ	73%	4.27	6,100	86	3.9	...	...	..
			246	152	170	110	1.015	2	0	40%	2.58	7,100	651	35.2	148.9	359	20
14	M	60	220	132	205	112	1.010	3	1	58%	2.96	6,600	146	6.6	....	...	..
15	M	75	240	140	170	80	1.022	2	2	82%	4.77	5,000	44	1.6	....	585	84
			...	...	...	...	.....	..	..	75%	4.50	18,200	110	3.0	....	537	50
16	F	57	300+	240	190	70	1.018	2	1	70%	4.24	7,000	102	1.9	....	568	63
17	M	22	170	112	118	80	1.030	3	3	76%	4.56	9,000	49	2.5	....	780	60
			215	160	170	118	1.013	3	0	60%	2.98	9,800	657	17.0	....	495	52
18	F	37	240	144	190	130	1.016	4	2	60%	3.04	12,000	252	6.4	....	...	..
19	F	23	278	205	235	160	1.012	4	0	58%	3.46	10,800	36	1.9	....	...	..
20	M	45	236	160	186	100	1.016	3	1	64%	3.68	19,600	216	9.6	....	...	48.5
21	M	30	230	165	170	128	1.013	3	0	17.2 Gm.	5.20	11,200	20	....	....	603	..
22	M	39	220	156	158	94	1.012	3	2	40%	2.48	20,800	444	20.0	....	479	21.7
23	M	40	160	80	112	70	1.030	0	0	15.9 Gm.	4.56	12,100	...	....	....	...	..
			180	120	170	110	1.016	2	1	60%	3.33	17,200	132	2.4	....	...	..
24	M	39	245	150	130	100	1.013	3	2	58%	3.03	19,800	243	9.2	18.9	462	46.6
25	M	56	250	135	160	90	1.014	3	3	45%	2.42	9,100	318	16.0	....	...	..
26	M	42	225	155	170	120	1.030	3	0	88%	4.20	9,300	40	1.5	....	...	..
			240	160	190	110	1.020	4	1	12.3 Gm.	3.76	13,200	190	3.0	10.5	...	..
27	M	37	244	162	168	106	1.038	4	4	13.3 Gm.	4.69	10,200	38	....	5.1	...	..
			206	140	136	92	1.019	4	4	7.6 Gm.	2.29	18,000	232	13.6	35.8	396	36.2
28	M	56	190	130	130	90	1.011	2	1	71%	3.33	9,800	303	23.0	26.5	520	26.8
29	F	52	160	100	...	...	.....	..	..	76%	4.50	7,000	48	1.8	5.9	...	..
			280	175	154	100	1.026	4	0	58%	3.14	20,100	256	....	....	...	..
30	F	26	160	110	120	70	1.027	3	1	79%	4.67	7,500	18	1.1	....	...	60.0
			190	120	180	115	1.025	4	1	14.7 Gm.	4.56	8,200	18	....	....	...	..
			240	160	184	110	1.025	2	2	80%	4.73	9,200	28	1.6	6.4	...	..
			240	150	170	110	1.000	3	0	15.2 Gm.	....	.....	28	1.2	6.8	561	47.5
			220	142	196	120	1.011	4	3	14.5 Gm.	4.85	17,250	34	8.4	....	...	24.7
			250	145	...	...	.....	..	..	....	....	.....	86	2.4	9.7	503	28.7
31	F	37	138	98	...	...	1.026	2	1	63%	....	8,300	...	....	....	...	..
			155	115	...	...	1.025	1	2	60%	3.75	10,200	...	....	....	...	..
			175	120	140	100	1.024	1	0	70%	4.76	8,500	14	....	....	...	12.6
			250	140	230	130	1.019	4	2	....	....	.....	42	....	....	...	..
32	F	35	245	160	144	90	1.018	4	3	12.6 Gm.	4.04	8,600	28	1.2	3.9	560	..
			...	...	...	...	.....	..	..	13.5 Gm.	....	.....	30	....	4.6	...	..
			...	...	...	...	.....	..	..	7.1 Gm.	1.98	7,200	246	12.8	31.4	569	37.2
33	M	32	350+	190	244	162	1.009	3	3	12.3 Gm.	4.06	21,700	108	3.8	....	479	46.6
34	M	52	220	130	166	88	1.020	1	0	97%	4.53	7,800	28	....	....	...	..
			230	135	...	...	1.014	0	0	15.9 Gm.	....	.....	24	....	5.8	...	..
			...	...	...	...	1.011	3	2	....	....	.....	...	....	....	...	..
35	M	29	240	150	164	75	1.021	3	4	51%	2.34	6,400	492	17.2	17.0	520	62.6
36	M	54	220	150	160	110	1.014	4	1	14.5 Gm.	3.83	8,700	144	5.6	13.9	479	53.2
37	M	48	260	150	176	100	1.015	3	3	7.6 Gm.	2.47	11,000	402	14.4	16.5	...	10.6
38	M	54	290	190	184	110	1.014	3	1	7.0 Gm.	3.71	8,700	285	8.4	17.7	611	32.4
39	M	46	244	150	140	80	1.013	4	2	14.9 Gm.	3.74	6,600	64	....	7.7	...	69.2
40	F	47	270	170	210	116	1.014	2	1	15.2 Gm.	4.70	6,200	126	4.8	4.4	...	..
41	M	47	130	80	...	...	1.023	2	2	80%	4.54	8,100	38	1.8	....	...	..
			120	80	...	...	1.025	2	1	15.7 Gm.	4.30	8,200	34	....	....	...	..
			212	152	134	78	1.017	2	1	89%	3.75	6,100	38	....	5.5	...	..
			250	160	176	100	1.016	4	4	9.0 Gm.	3.39	7,300	162	8.1	11.7	...	58.9
42	M	57	230	175	146	108	1.021	3	1	14.5 Gm.	3.57	6,400	116	....	6.0	575	42.8
43	M	55	240	152	178	98	1.031	4	2	89%	4.56	8,300	42	....	4.3	...	..
44	F	41	230	125	184	102	1.016	0	0	95%	....	6,800	...	....	....	...	..
			245	120	...	...	.....	..	..	11.7 Gm.	4.40	5,000	64	2.2	6.5	528	54.1
			250	150	165	85	1.020	4	1	9.5 Gm.	3.53	30,900	192	5.2	12.2	455	26.8
45	F	7	238	190	136	74	1.030	3	4	11.1 Gm.	3.22	29,100	86	1.4	3.8	...	..
46	M	34	204	152	150	100	1.015	3	2	101%	4.09	6,700	48	....	5.9	...	..
			260	160	116	72	1.015	4	4	....	....	.....	510	26.4	61.9	445	54.1
47	M	50	136	94	...	...	1.020	0	0	15.7 Gm.	....	8,300	32	....	....	...	..
			190	118	174	114	1.019	0	0	16.2 Gm.	4.12	4,900	...	....	....	...	..
			258	170	180	110	1.017	3	2	77%	4.31	9,100	168	6.0	8.7	515	47.5
48	F	44	250	175	180	110	1.022	4	1	13.3 Gm.	4.87	19,600	30	....	4.0	...	..

* Hemoglobin is expressed in grams per hundred cubic centimeters of blood. The remaining values represent the per cent of hemoglobin by the Dare method.

Analysis of physical observations was directed especially to the cardiovascular system, and the results were in accord with the analysis made by Keith, Wagener and Kernohan. Marked elevation of blood pressure was observed in all cases. The maximal systolic reading varied from 170 to 350 mm. of mercury, and the maximal diastolic, from 100 to 240 mm. In cases 31, 41 and 47 the blood pressure was normal on the first visit to the clinic, but on subsequent visits it was found to be elevated (table 2). Clinical evidence of anemia was noted infrequently. There was palpable enlargement of the thyroid gland in 3 cases. The grade of peripheral vascular sclerosis as determined by palpation of the brachial and radial arteries varied from 1 to 3. It was mild in 4 cases, moderate in 13 and marked in 20. Arterial occlusion in the extremities did not occur.

A diffuse purpuric eruption was noted in 6 cases. Meakins [26] has called attention to the purpuric manifestations and other hemorrhagic phenomena accompanying conditions associated with hypertension. He expressed the belief that these manifestations are caused by arteriolar or capillary vasoconstriction leading to slowing of the blood stream, or "prestasis," with subsequent diapedesis of erythrocytes into surrounding tissues.

Tachycardia was present in 42 of the 48 cases, and the heart was measurably enlarged to percussion in the same number of cases. Extrasystoles were encountered in 8 cases, auricular fibrillation in 4, gallop rhythm in 9 and pulsus alternans in 3.

The aortic second sound was accentuated in 31 cases and the pulmonic second sound in 7. Cardiac murmurs were heard in the majority of cases. In 28 cases there was an apical systolic murmur, and in 19, an aortic systolic murmur. An apical diastolic murmur was audible in 5 cases, and an aortic diastolic murmur in 2. A pericardial friction rub was heard in 10 cases. In 38 cases the patients exhibited signs of cardiac decompensation. The spleen was palpable in 2 cases.

Cheyne-Stokes respiration was noted in 20 cases. Muscular twitchings occurred in 11 cases and generalized convulsions in 4. Twelve patients had signs of involvement of the central nervous system. Signs of cerebrovascular accident were present in 11 cases. In case 32 there was a history of recurrent facial palsy, and the neurologic signs were those of facial paralysis without hemiplegia. In case 36 a tumor of a temporal lobe was suspected.

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26. Meakins, J. C.: Arteriolar Infarction, Ann. Int. Med. **8**:661-668 (Dec.) 1934.

The retinal features characteristic of malignant hypertension as described by Wagener and Keith, with narrowing and sclerosis of the retinal arterioles and edema of the optic disks, were present in all 48 cases.

LABORATORY DATA

The specific gravity of the urine varied from 1.000 to 1.038. In 16 cases the specific gravity exceeded 1.020. In cases 17, 23, 26, 27, 30, 31 and 41 it exceeded 1.020 on early admission to the clinic but was lower than 1.020 on subsequent determinations. Albuminuria varied in grade from 1 to 4. In only 5 cases was the urine free from albumin. In the majority of cases casts were present in the urine, and hematuria varied in grade from 1 to 4.

If 80 per cent hemoglobin, or 12 Gm. of hemoglobin per hundred cubic centimeters of blood, and 4,000,000 erythrocytes per cubic millimeter of blood are considered to be the lower limits of normal, it will be noticed that anemia in varying degree was present in the great majority of instances. It is interesting to observe that the leukocyte count exceeded 9,000 per cubic millimeter of blood for more than half the patients.

The serologic tests for syphilis gave negative results in 44 cases. In cases 12, 38 and 31 the results were strongly positive, and in case 37 the reaction was indeterminate. In case 12 the results of tests for syphilis performed on the spinal fluid were also strongly positive.

If 40 mg. of urea per hundred cubic centimeters of blood is considered to be the upper limit of normal, the terminal value for 43 patients was elevated. In 7 cases the concentration of urea in the blood varied from 40 to 100 mg. per hundred cubic centimeters. Determinations of "terminal blood urea" in 25 cases revealed between 100 and 300 mg. per hundred cubic centimeters. In these 32 cases (7 plus 25) it is difficult to estimate how much of the elevation in the concentration of urea can be accounted for on the basis of renal insufficiency and how much was caused by congestion in the kidneys occurring as part of the picture of congestive heart failure. In 11 cases the value for blood urea exceeded 300 mg. per hundred cubic centimeters. The value for the terminal concentration of blood creatinine was more than 2 mg. per hundred cubic centimeters in 35 cases.

Determinations of the values for serum sulfate were made in 23 cases. In 19 the terminal value was above the upper limit of normal (5.5 mg. per hundred cubic centimeters). In case 13, the value increased terminally to 148.9 mg. per hundred cubic centimeters, which is the highest figure for serum sulfates on record at the Mayo Clinic.

The value for plasma chlorides was normal in the majority of cases. The carbon dioxide–combining power of the plasma was measured in 31 cases. In only 13 cases did the value fall below 40 volumes per cent, indicating the presence of significant acidosis.

The rate of excretion of phenolsulfonphthalein in the urine was measured in 20 cases. In 11 cases, in two hours' time the patient excreted 50 per cent or more of the dye injected. In cases 8, 10, and 17 no dye was recovered in the urine.

TABLE 3.—*Rates and Axis Deviations: Forty-Nine Electrocardiograms Representing Thirty-Five Patients Having Diffuse Arteriolar Disease with Hypertension Group 4*

Rate	Tracings, Number	Axis Deviation	Tracings, Number
Sinus bradycardia	6	Left	39
Sinus rhythm	26	Right	1
Sinus tachycardia	17	None	9
Totals	49		49

TABLE 4.—*Alterations in the RT Segments and T Waves: Forty-Nine Electrocardiograms Representing Thirty-Five Patients Having Diffuse Arteriolar Disease with Hypertension Group 4*

	Deviation	I	II	III	IV*
RT Segment	Depressed	37	21	5	3
	Isoelectric	12	24	18	0
	Elevated	0	4	26	0
	Total	49	49	49	3
T Waves	Inverted	24	14	16	2
	Diphasic	12	16	3	1
	Isoelectric	1	2	0	0
	Upright	12	17	30	0
	Total	49	49	49	3

* Only three tracings of deviation IV were made.

The laboratory data for each patient are given in table 2.

Forty-nine electrocardiograms representing 35 cases were studied, and the results are given in tables 3 and 4. It is of interest that in case 8 right axis deviation was observed. In this case there was a presystolic murmur which was transmitted to the tricuspid area, but no other signs of rheumatic heart disease were present. However, at necropsy the mitral valves were found to be markedly thickened, and there was hypertrophy of both ventricles, with marked dilatation of the right.

The tracings in cases 12 and 15 showed T waves in derivations I and II suggestive of coronary occlusion, but this condition was not confirmed either clinically or pathologically. In case 48, diminished Q waves were noted in derivation IV. The sudden death of the patient suggested

the presence of coronary occlusion or cerebral accident, but at necropsy no signs of coronary thrombosis were discovered.

Although the results were variable, table 4 indicates that the majority of tracings showed depression of the RT segment, that inverted T waves predominated in derivation I, that a depressed or isoelectric RT segment predominated in derivation II and that the majority of tracings showed an elevation of the RT segment, with upright T waves, in derivation III.

PATHOLOGIC DATA

The time from the onset of symptoms to death varied from two months to two years and eight months, the average being eleven months. Postmortem examinations were performed in all 48 cases. One patient (case 45) died elsewhere, and pathologic material was sent to the clinic by the pathologist who performed the necropsy.

The cases were placed in four groups on the basis of the conditions causing death: cerebral, cardiac, renal and mixed. Seven patients died of cerebrovascular accident; 12 died of cardiac failure. Twenty-three patients died of cardiac and renal failure; 1 died of cerebral accident and renal insufficiency, and 2 died of cerebral, cardiac and renal failure. One patient (case 5) died after an attack which strongly suggested coronary occlusion, but this was not confirmed at necropsy. One patient (case 15) died of massive hemorrhage from a duodenal ulcer. In 1 instance the manner of death of the patient was unknown. In 1 instance the patient was found dead; whether death occurred as a result of cardiac failure or of cerebral accident could not be determined.

In 47 cases the weight of the heart ranged from 390 to 870 Gm., the average being 567 Gm. Hypertrophy of the left ventricle was conspicuous in all cases.

One patient (case 45) was 7 years of age. The heart weighed 180 Gm., and there was marked hypertrophy of the left ventricle, the wall being 24 mm. in width at its thickest point. Signs of pericarditis were present in 13 cases. In cases 17, 18, 19 and 41 no exudate was demonstrable, but the pericardial fluid was increased in amount and was cloudy. Clinical signs of pericarditis were confirmed at necropsy in 7 of the 9 cases in which exudate was present. One patient (case 3) had a suggestive pericardial rub prior to death, but no evidence of pericarditis was observed at necropsy.

Aortic sclerosis ranged from mild to severe. In 16 cases sclerosis was mild; in 27, moderate, and in 4, severe. Sclerosis of the coronary arteries was mild in 20 cases, moderate in 20 and severe in 7. Coronary sclerosis could not be demonstrated in case 45.

TABLE 5.—*Pathologic Data: Forty-Eight Patients Having Diffuse Arteriolar Disease with Hypertension Group 4*

Case	Duration of Life After Onset of Symptoms, Months	Weight of Heart, Gm.	Pericarditis, Pathologic	Pericarditis, Clinical	Coronary Sclerosis, Grade	Aortic Sclerosis, Grade	Infarction	Combined Weight of Kidneys, Gm.	Arterioles of Myocardium, Ratio Wall to Lumen	Arterioles of Pectoral Muscle, Ratio Wall to Lumen
1	6	400	..	..	1—	1—	.....	270	1:2.06	.....
2	12	838	..	..	3	3+	Patchy, left ventricle	302	1:1.91	.....
3	8	475	..	?	1	2	.....	247	1:2.07	.....
4	2	623	+	+	2	1+	.....	254	1:2.06	.....
5	8	715	..	..	2	2	.....	194	1:1.96	.....
6	6	496	..	..	3	2+	.....	206	1:1.79	.....
7	3	695	..	..	1+	1+	.....	337	1:1.81	.....
8	8	641	+	..	1	1	.....	348	1:2.07	.....
9	4	870	..	..	1	2	.....	...	1:1.82	1:1.36
10	24	540	..	..	2	2	.....	285	1:1.96	.....
11	12	460	..	..	1+	2	.....	120	1:1.97	.....
12	7	474	..	..	1	1	.....	233	1:1.97	1:1.13
13	32	618	+	+	2	1	.....	243	1:2.09	1:0.99
14	6	524	..	..	2+	2	Patchy, left side of septum	...	1:1.84	1:1.51
15	4	570	..	+	3	3+	.....	221	1:1.82	.....
16	7	465	..	..	2	3+	.....	225	1:1.71	.....
17	13	445	*	+	2	1—	.....	204	.....	1:1.12
18	2	464	*	..	3	3	.....	218	.....	1:1.15
19	18	630	*	..	2	2+	.....	248	1:1.99	1:1.36
20	3	486	..	..	2	2	.....	305	1:1.93	.....
21	29**	525	+	..	2	2+	.....	200	1:1.98	1:1.37
22	24	675	..	..	3	1+	.....	385	1:2.11	1:1.25
23	4	471	..	..	..	1—	.....	213	1:2.09	.....
24	18	564	..	..	1+	2	.....	388	1:1.91	.....
25	24	730	+	..	1	2	.....	309	1:2.09	.....
26	4	650	..	..	2	2	.....	254	1:2.04	.....
27	20	534	+	+	1	2+	.....	341	1:1.81	.....
28	2	632	..	..	2	2	.....	216	1:1.97	1:1.98
29	24	565	+	+	1	2	.....	289	1:1.96	.....
30	21**	390	+	..	2	1+	.....	200	1:1.81	.....
31	?	394	..	..	2	2	.....	285	1:2.02	1:1.41
32	12	460	..	..	2	1+	.....	230	1:1.99	.....
33	4	722	..	..	1	1	.....	270	.....	1:1.36
34	17	727	+	..	1+	2	.....	346	1:1.94	1:1.41
35	8	405	+	+	1	1+	.....	144	1:1.99	.....
36	9	651	..	..	2	2	.....	324	1:2.04	1:1.18
37	6	656	..	..	1+	2	.....	196	1:1.89	1:1.43
38	12	778	..	..	1	2+	.....	276	1:1.81	.....
39	6	549	..	..	2	2	.....	280	1:2.14	.....
40	6	487	..	..	3	2	.....	321	1:2.10	.....
41 †	9	627	*	..	2+	2+	Septum and anterior portion of left ventricle	366	1:2.12	1:1.43
42	6	554	..	..	2+	2+	.....	260	1:1.88	.....
43 †	18	505	+	..	2	2+	.....	140	1:1.86	.....
44	13	530	+	+	1	1	.....	237	1:1.87	1:1.28
45	13**	180	..	..	1	..	.....	130	1:1.72	.....
46	9	528	+	+	1+	1+	.....	210	1:1.89	1:1.37
47	8	730	..	..	2	1+	Patchy, left ventricle	207	1:1.81	1:1.39
48	4	578	..	..	1	2	Patchy, septum	326	1:2.02	1:1.23

* No definite exudate but cloudy pericardial fluid.

** Patient died at home.

† In cases 41 and 43 the anterior descending branch of the left coronary artery was occluded.

Occlusion of the coronary arteries occurred in 2 cases (41 and 43), and in both instances the anterior descending branch of the left coronary artery was the vessel affected. In neither case was there a history of coronary occlusion, nor was there electrocardiographic evidence of such an accident. Acute myocardial infarction was demonstrable in the septum and in the anterior apical portion of the left ventricle in case 41. Four patients (cases 2, 14, 47 and 48) had patchy fibrous tissue replacement in the septum, distributed in a manner characteristic of chronic fibrosis of the myocardium.

The combined weight of the kidneys varied from 120 to 388 Gm., the average weight being 256.6 Gm. In only 6 cases was the combined weight of the kidneys less than 200 Gm. Keith, Wagener and Kernohan reported that in their series the kidneys exhibited varying degrees of atrophy but that in most cases the combined weight was only slightly below normal. In all our cases the surfaces of the kidneys presented a granular appearance, with pitting and scarring. The significant pathologic data are given in detailed form in table 5.

HISTOLOGIC STUDIES

Method.—Histologic study was made of the myocardium in 45 of the 48 cases in the present series. Material for controls was obtained from 90 patients who did not have hypertension or cardiac enlargement (table 6). No patients were accepted for controls who had a maximal blood pressure exceeding 140 mm. of mercury systolic or 90 mm. of mercury diastolic. The normal weight of the heart in each case was computed according to the formulas of Smith.[27] Each patient was selected in such a manner that the actual weight of the heart fell between the minimal and maximal theoretic cardiac weights computed from the theoretic normal body weight of the patient.

Fifteen control subjects were selected for each of the six decades represented in the hypertensive series (table 7). No controls were used for 1 patient (case 45), because she was only 7 years of age. At that age the factor of growth complicates the picture, and it is impossible to establish theoretic normal cardiac weights for the first decade of life.

Sections were cut from the left ventricle, the right ventricle and the interventricular septum. All specimens were fixed in solution of formaldehyde, embedded in paraffin, cut and stained with hematoxylin and eosin, by Van Gieson's method or with elastin H stain. A number of sections were stained according to the Mallory-Heidenhain method.

Particular study was made of the arterioles, i. e., vessels the outside diameter of which was between 25 and 100 microns. This is the criterion

27. Smith, H. L.: The Relation of the Weight of the Heart to the Weight of the Body and of the Weight of the Heart to Age, Am. Heart J. **4**:79-93 (Oct.) 1928.

for identification of an arteriole used by Kernohan, Anderson and Keith in their study of the arterioles of pectoral muscle.

Results.—There were moderate but definite changes in the structure of the arteriolar walls in the majority of instances. Moderate thickening of the tunica media, with an increase in the nuclear elements, was seen; however, in no case could the presence of medial fibrosis be demonstrated (fig. 1 *A*). In relatively few arterioles evidence of necrosis

TABLE 6.—*Mean Wall to Lumen Ratio: Arterioles of Pectoral Muscle of Twenty Patients and Arterioles of Myocardium of Forty-Five Patients Having Diffuse Arteriolar Disease with Hypertension, Group 4, Compared with Arterioles of Persons Without Hypertension (Controls)*

Situation of Arterioles Studied	Hypertension			No Hypertension		
	Patients	Wall to Lumen Ratios (Variations)	Mean Ratio	Patients	Wall to Lumen Ratios (Variations)	Mean Ratio
Myocardium	45	1:1.72 to 1:2.02	1:1.95	90	1:2.04 to 1:2.16	1:2.09
Pectoral muscle	20	1:1.14 to 1:1.31	1:1.27	58	1:1.77 to 1:2.72	1:1.97

TABLE 7.—*Mean Wall to Lumen Ratios by Decades of Life: Arterioles of the Myocardium of Forty-Five Patients Having Diffuse Arteriolar Disease with Hypertension Group 4 and Arterioles of the Myocardium of Ninety Persons Without Hypertension (Controls)*

Age by Decades	Hypertension		No Hypertension	
	Patients	Mean Wall to Lumen Ratio	Patients	Mean Wall to Lumen Ratio
0–9	1	1:1.72	..	.....
10–19	0	.....	..	.....
20–29	4	1:1.94	15	1:2.05
30–39	8	1:1.96	15	1:2.09
40–49	17	1:2.02	15	1:2.04
50–59	12	1:1.90	15	1:2.16
60–69	2	1:1.82	15	1:2.06
70–79	1	1:1.82	15	1:2.09
Total	45	1:1.95*	90	1:2.09*

* Mean wall to lumen ratio for the entire group in each column.

was seen in the tunica media (fig. 1 *B*). Some increase in perivascular connective tissue was noted. The elastin H stain disclosed some degree of hypertrophy of the internal elastic lamina, with mild to moderate splitting in most cases (fig. 2).

In a number of blood vessels there were apparent mild proliferation of the endothelial cells (fig. 3 *A*) and intimal hyperplasia; however, in only a few cases was there intimal thickening sufficient to be significant (fig. 1 *B*). Partial occlusion of the arteriolar lumen was noted in a few instances, but in none was the lumen completely occluded.

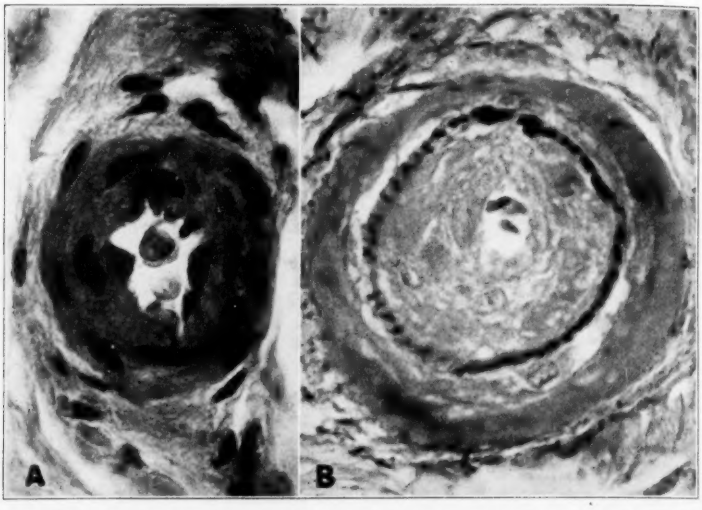

Fig. 1.—*A*, section of an arteriole (case 47). Thickening of the wall is evident, and the medial nuclei are increased in number. Hematoxylin and eosin; × 850. *B*, section of an arteriole (case 11), showing an extreme degree of intimal thickening, with almost complete obliteration of the lumen; evidence of medial necrosis can be noted. Elastin H; × 735.

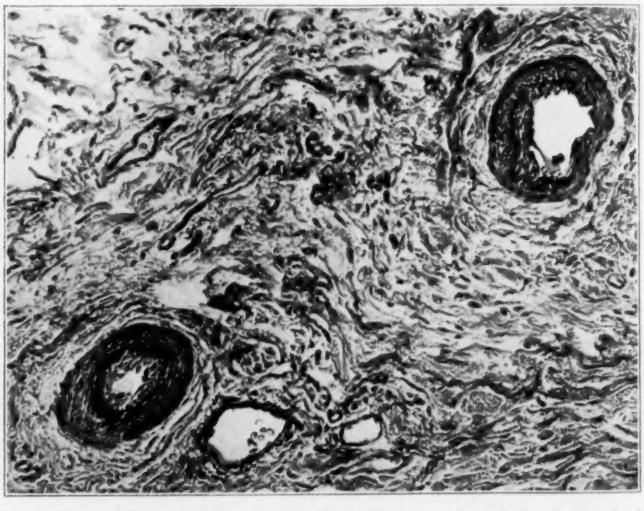

Fig. 2 (case 43).—Section of arterioles. Hypertrophy of the internal elastic lamina can be noted in the lower vessel, and intimal thickening is conspicuous in both vessels. Elastin H; × 180.

One of the most striking features was the relative frequency with which fibrous tissue replacement in the myocardium occurred in the hypertensive group as compared with the nonhypertensive group, irrespective of the age of the patient or the degree of coronary arteriosclerosis present (fig. 3*B*). Varying degrees of fibrosis, ranging from mild to moderate, occurred in several of the nonhypertensive patients, but in general there was a definite increase of fibrosis in the myocardiums of hypertensive patients compared with that in the myocardium of nonhypertensive patients.

The most noticeable observation was the lack of consistency of the structural changes in the arterioles. Not only was there a wide variation

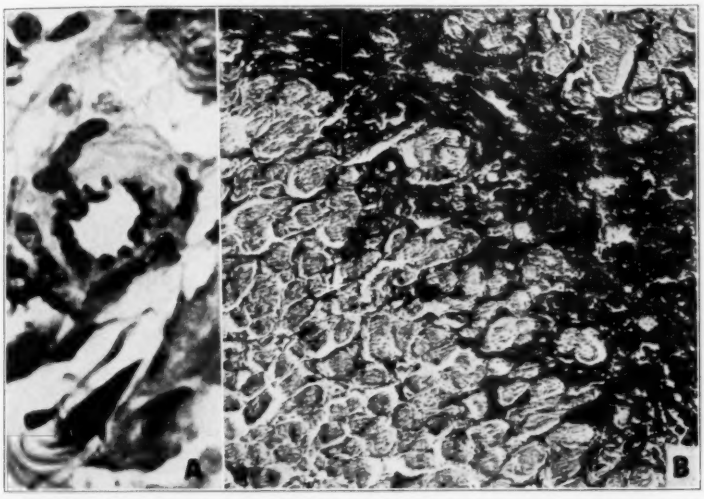

Fig. 3.—*A*, section of an arteriole (case 45) showing apparent mild proliferation of endothelial cells. Van Gieson; × 860. *B*, extensive diffuse myofibrosis in the myocardium (case 9). Van Gieson; × 195.

in the findings from case to case, but there was a striking variation among the different arterioles in the same case and in different segments of the same arteriole (fig. 4).

The outside and inside diameters of the myocardial arterioles were measured in all cases, and the wall to lumen ratios were computed. This was done after the method described by Kernohan, Anderson and Keith, and a Bausch and Lomb micrometer was used. Estimations were made on six arterioles in each case, and the mean wall to lumen ratio was computed. Only those vessels which were cut in cross section were considered suitable for measurement.

It was found that in the series of nonhypertensive patients the mean wall to lumen ratio for arterioles of the myocardium was 1 : 2.09, with

variations from 1 : 2.04 to 1 : 2.16. In the series of cases of malignant hypertension the mean ratio was 1 : 1.95, with variations from 1 : 1.72 to 1 : 2.02 (table 6). There was no significant relation between the mean wall to lumen ratio and the age of the patient in either the normal or the hypertensive group (table 7). It should be stated that it was impossible to distinguish on the basis of the wall to lumen ratio between nonhypertensive patients and patients with malignant hypertension.

Figures 5 and 6 show these results in graphic form. In figure 5 the mean wall to lumen ratios are plotted as abscissas against the percentile frequencies as ordinates. It is apparent that there is con-

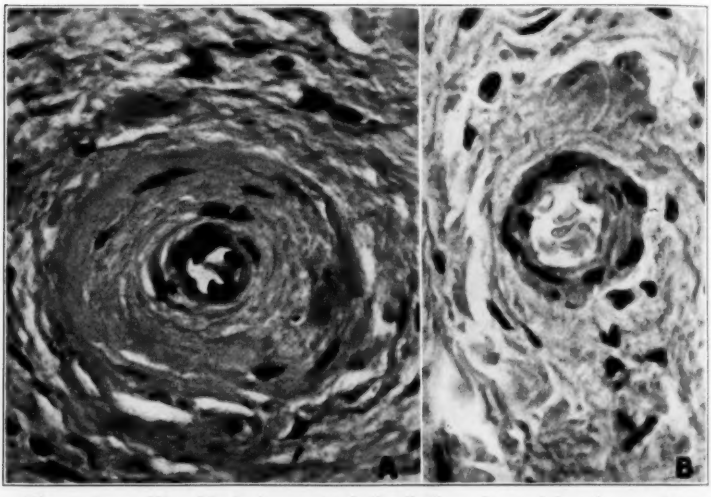

Fig. 4 (case 43).—Marked segmental distribution of arteriolar changes in the myocardium. *A*, section of an arteriole. The apparent marked thickening of the wall of the vessel is the result of increase in perivascular connective tissue. Hematoxylin and eosin; × 605. *B*, same vessel shown in *A*, with several sections removed. Van Gieson; × 605.

siderable overlapping between the mean wall to lumen ratios for arterioles of the nonhypertensive patients and those for arterioles of the hypertensive group, especially when the ratio falls between 1 : 1.8 and 1 : 2.1.

In figure 6 the widths of the arteriolar lumens in microns have been plotted as abscissas against the mean thicknesses of the arteriolar wall as ordinates. Each point represents the mean thickness of the wall of all vessels having the same width of lumen. Lines were drawn through these points to indicate the mean about which the values for hypertensive and those for the nonhypertensive arterioles are arranged. Because the angle formed by this line and the ordinate represents the mean wall to lumen ratio, it is apparent that the nearer this line

approaches the ordinate, the smaller is the mean wall to lumen ratio. It follows that the greater the total diameter of the arteriole, the greater is the difference in mean ratio between the hypertensive and the nonhypertensive arterioles.

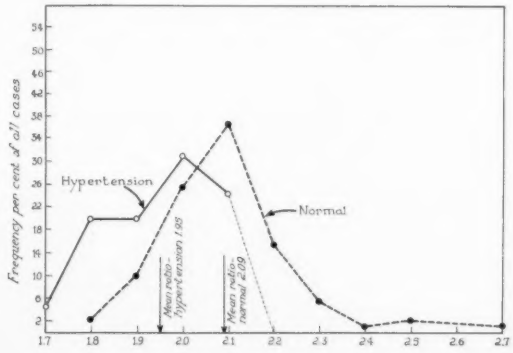
Frequency per cent of all cases
Hypertension
Normal
Mean ratio - hypertension 1.95
Mean ratio - normal 2.09
1.7 1.8 1.9 2.0 2.1 2.2 2.3 2.4 2.5 2.6 2.7

Fig. 5.—Percentile frequency distribution and wall to lumen ratio for the arterioles of the myocardium (patients with malignant hypertension and persons without hypertension).

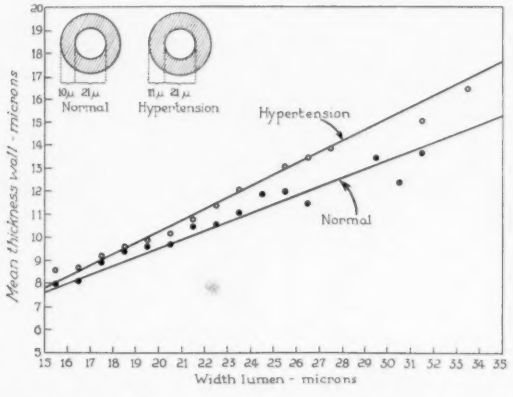
Mean thickness wall - microns
10μ 21μ
Normal
11μ 21μ
Hypertension
Hypertension
Normal
13 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35
Width lumen - microns

Fig. 6.—Thickness of the wall and width of the lumen in the arterioles of the myocardium (patients with malignant hypertension and persons without hypertension).

The diagrams in the upper left hand corner of figure 6 represent mean measurements of the diameters of the wall and lumen of the entire series, for both the hypertensive and the nonhypertensive group.

As a comparative study, the wall to lumen ratios of the arterioles of pectoral muscle were computed for 20 of the 45 patients with malignant hypertension and for 58 nonhypertensive patients. The mean wall to

lumen ratio of control subjects was 1 : 1.97, which compares favorably with Kernohan's [21] figure of 1 : 2.0. In the hypertensive group the mean wall to lumen ratio was 1 : 1.27 (table 6). The pathologic changes in

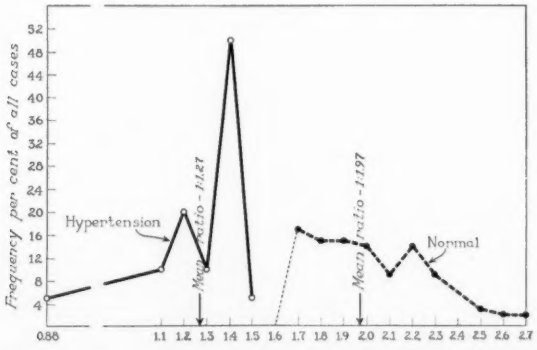

Fig. 7.—Percentile frequency distribution and wall to lumen ratios for arterioles of pectoral muscle (patients with malignant hypertension and normal persons).

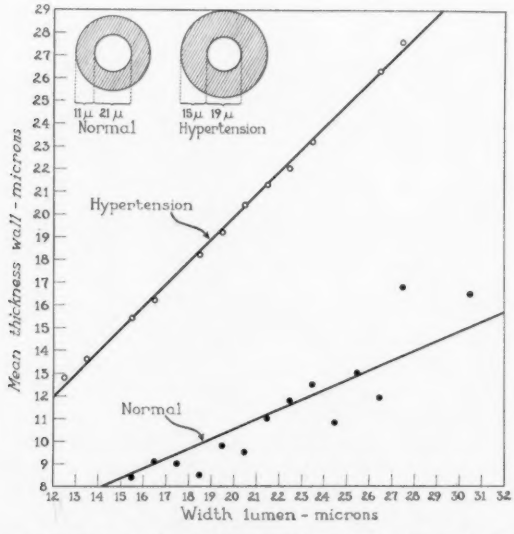

Fig. 8.—Thickness of the wall and width of the lumen in arterioles of the pectoral muscle (patients with malignant hypertension and normal persons).

the arterioles themselves were similar to those described by Kernohan, Anderson and Keith. This comparison emphasizes the fact that arteriolar changes do occur in the myocardium in the presence of malignant hyper-

tension, although they are less marked than in skeletal muscle and other organs.

Figures 7 and 8 have been constructed in the same manner as figures 5 and 6 and represent the relation between the arterioles of the pectoral muscle in the hypertensive group and those in the nonhypertensive group.

COMMENT

The results of this study indicate that in the presence of diffuse arteriolar disease with hypertension group 4, structural changes in varying degrees of severity occur in the arterioles of the myocardium. The exact nature of these changes has been a subject for considerable controversy during the years since Bright first suggested the existence of a relation between vascular changes and cardiorenal disease. Johnson's original belief that changes in the tunica media are essentially proliferative has been substantiated by Ewald, Fischer and Schlayer,[28] Brogsitter,[29] Evans,[30] Kernohan and his associates, Moritz and Oldt, Pilcher and Schwab and others. The belief that the changes are degenerative finds support in the work of Gull and Sutton, Jores, Fishberg and others.

In the foregoing study, wide variation from case to case was noted in the nature and degree of change. Increase in the medial nuclei seemed to be an early change, with hyperplasia of the internal elastic lamina, intimal proliferation and degenerative changes occurring later in the process. It is a significant fact that structural changes in the myocardial arterioles were not observed in all cases and that, when they did occur, the changes were similar to those occurring in other organs in the same case, although less pronounced.

The analysis of the clinical features in this series of cases substantiates the statement of Keith and his co-workers [1] that the syndrome of malignant hypertension is a clearcut clinical entity and that the clinical picture may be characterized by symptoms predominantly cerebral, cardiac or renal or by any combination of the three. This conception is in accordance with the conclusion of Gull and Sutton that the clinical history varies from case to case according to the organ or organs most severely affected.

The presence of diffuse fibrosis in the myocardium in increased degree among the hypertensive patients is in accordance with the

28. Fischer, H., and Schlayer: Arteriosklerose und Fühlbarkeit der Arterienwand, Deutsches Arch. f. klin. Med. **98**:164-185, 1910.

29. Brogsitter, A. M.: Zur Anatomie der Splanchnikusgefässe beim Hochdruck, München. med. Wchnschr. **2**:1049-1051 (Aug. 1) 1924.

30. Evans, G.: A Contribution to the Study of Arterio-Sclerosis, with Special Reference to Its Relation to Chronic Renal Disease, Quart. J. Med. **14**:215-282 (April) 1921.

observations of Fahr,[31] who explained this phenomenon on the basis of hypertrophy of the cardiac musculature and insufficient circulation and supply of oxygen to the hypertrophied muscle cells, with resultant necrosis and fibrosis.

Not only was there wide variation in the occurrence and degree of severity of the histologic changes among individual patients, but there was a striking difference in the degree of involvement between different vessels of the same patient and between different segments of the same vessel. Moritz and Oldt observed similar segmental distribution in their study of the pathologic changes occurring in the arterioles of skeletal muscle of hypertensive patients.

From the evidence presented here and from data collected by others, it appears that malignant hypertension is a diffuse arteriolar disease in every sense of the term and that no organ which is subjected to elevation in systemic blood pressure can escape entirely. Why structural changes in the arterioles of the myocardium do not progress at the same rate or to the same degree as do similar changes in the arterioles of other organs is a question which has yet to be answered.

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31. Fahr, G.: The Heart in Hypertension, J. A. M. A. **105**:1396-1400 (Nov. 2) 1935.

FATTY DEGENERATION OF THE HEART CAUSING MYOCARDIAL INSUFFICIENCY

REPORT OF A CASE

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Fatty degeneration of the heart is a retrogressive condition in which fat droplets are found in the myocardial sarcoplasm. It is usually secondary to such conditions as myocarditis, pericarditis, coronary arteriosclerosis, myocardial insufficiency, starvation, anemia, fever, phosphorus or arsenic poisoning, diphtheria, scarlet fever, typhoid fever and various other diseases but has been noted to occur without any demonstrable cause.[1] The condition is common, especially in minor degrees.

Concerning the functional significance of fatty degeneration of the heart there is no unanimity of opinion. Lewis[2] stated: "Fatty heart should not be diagnosed. . . . In severe diphtheria the cardiac muscle may be so degenerate with fatty particles that it is throughout of a pure yellow colour, yet the heart continues beating. Because diffuse fatty degeneration occurs in the senile heart, or in coronary artery disease, that is no reason for regarding fat in the heart as a cause of sudden death. Equal change is found in the heart of pernicious anaemia and here sudden death is most unusual."

Willius[3] stated: "Fatty degeneration does not produce cardiac insufficiency." MacCallum[4] wrote that "the presence of fatty degeneration seems to have very little detrimental effect upon the function of the heart." Herrmann[5] concluded that fatty degeneration occurring during the course of infections is "rarely sufficient to produce heart failure." Welch,[6] in studying animals kept for a long time at fever heat, found

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1. Delafield, F., and Prudden, T. M.: A Text-Book of Pathology, ed. 15, New York, William Wood & Company, 1931, pp. 619-620.

2. Lewis, T.: Diseases of the Heart, ed. 2, New York, The Macmillan Company, 1937, p. 250.

3. Willius, F. A.: The Heart in Obesity, Mod. Concepts Cardiovasc. Dis., 1938, vol. 7, no. 9.

4. MacCallum, W. G.: A Text-Book of Pathology, ed. 6, Philadelphia, W. B. Saunders Company, 1936, p. 452.

5. Herrmann, G. R.: Synopsis of Diseases of the Heart and Arteries, St. Louis, C. V. Mosby Company, 1936, p. 170.

6. Welch, cited by MacCallum.[4]

abundant deposition of fat in their hearts but no special functional alteration.

On the other hand, Delafield and Prudden [1] noted that fatty degeneration of the heart may "lead to thinning of the walls, or to rupture of the heart, or to inability to fulfil its functions" and that "it is not infrequently a cause of sudden death." Muir [7] stated that the importance of fatty degeneration has been "much exaggerated," even though "the reserve power is diminished and the heart may suddenly fail."

Mönckeberg [8] went so far as to state that fatty degeneration of the myocardium cannot be regarded as an unimportant lesion of the heart muscle, and that it may be cited as one of the causes of the development of heart failure. No specific cases were described.

This communication reports a case of chronic congestive heart failure in which autopsy revealed no explanation for the myocardial insufficiency except severe idiopathic fatty degeneration of the myocardium. Search of the literature has revealed no comparable case.

REPORT OF CASE

C. D., a white man aged 42, an office worker, who entered the Cleveland City Hospital Dec. 5, 1938, had been in excellent health until October 1937, when he first noted shortness of breath, weakness and edema of the ankles. Despite treatment, the symptoms became more marked, and in April 1938 he was forced to go to bed, where he remained until July. At this time he was sufficiently improved to return to work. The shortness of breath and edema returned, however, and became increasingly severe, so that he was admitted to the hospital. There was no history of any sort of pain in the chest or of hypertension. The diet had been adequate and well balanced.

The patient's past and marital histories were not remarkable. He had never had scarlet fever, chorea, rheumatic fever or venereal disease. He was married and had two healthy children.

On physical examination the patient was found to be suffering from severe myocardial insufficiency. He was markedly dyspneic, edematous from the chest down and cyanotic. The veins of the neck were distended. The heart was considerably enlarged. There was gallop rhythm, the cardiac mechanism was normal and the rate was 120 beats per minute. There were rales at the bases of the lungs. The liver was enlarged and tender. The eyegrounds were normal. The blood pressure in millimeters of mercury was 110 systolic and 85 diastolic, and the temperature was 38 C.

Urinalysis revealed albumin, grade 3, and a specific gravity of 1.032. During the course in the hospital the albumin disappeared from the urine. The erythrocytes numbered 5,240,000 per cubic millimeter and the leukocytes 9,250 and the value for hemoglobin was 105 per cent. The Kline test for syphilis gave a negative result. The urea nitrogen content was 27.3 mg. per hundred cubic centimeters of blood. Fluoroscopic and roentgen studies of the heart and aorta showed

7. Muir, R.: Text-Book of Pathology, Philadelphia, J. B. Lippincott Company, 1924, p. 263.

8. Mönckeberg, J. G.: Die Erkrankungen des Myokards und des spezifischen Muskelsystems, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, vol. 2, pt. 3, p. 345.

the heart to be greatly enlarged in all directions and to have pulsations of very small amplitude. The electrocardiogram showed low voltage in all leads and an inverted T wave in leads II and III.

Despite treatment, the patient remained in marked congestive heart failure and was critically ill. He had a right pleural effusion which required aspiration three times. There were several episodes suggesting pulmonary infarction. The temperature varied between 37 and 41 C., the pulse rate between 90 and 140

Photomicrograph (scarlet red fat stain) showing the innumerable fine droplets of fat in the myocardial fibers. This section shows an area in which the involvement was relatively moderate. In many areas the droplets of fat were confluent. × 276.

beats per minute and the blood pressure between 84 and 122 systolic and 60 and 96 diastolic. The patient died December 26.

The initial clinical diagnosis was sclerosis of the coronary arteries with myocardial fibrosis and heart failure, but this was changed to acute isolated (Fiedler's) myocarditis shortly before death.

Autopsy Observations (*Dr. L. L. Terry*).—There was ample evidence of chronic myocardial insufficiency in the form of severe passive hyperemia of the viscera,

hydrothorax (on the right), edema of the legs and dilatation of the heart. There were recent infarcts in the lower lobes of both lungs and thrombi in the branches of the pulmonary artery to the right lung.

The heart weighed 405 Gm. It was remarkably soft and flabby. When placed on a flat surface it quickly flattened out into a shapeless mass. The myocardium was a peculiar pale brownish yellow. There were numerous small mural thrombi in the left ventricle. Otherwise the heart showed no abnormalities. The epicardium, endocardium, valves and coronary arteries were completely normal. The amount of subepicardial fat was slightly less than usual. The remaining viscera showed no significant changes other than hyperemia.

Microscopic examination of numerous sections from the heart showed the endocardium and epicardium to be normal. The myocardial fibers were large, pale, granular, vacuolated and severely fragmented, and the cross striations were obscure. The nuclei showed considerable variations in size, shape and staining affinities. There was no evidence of inflammation and no fibrosis, and the large and small arteries were normal.

Fat stain showed the myocardial fibers uniformly to contain innumerable fine droplets of fat (see accompanying illustration). In certain areas the droplets were arranged in longitudinal lines; in others the droplets were so abundant as to be confluent.

Microscopic examination of the other viscera confirmed the diagnoses made on gross examination. In addition, the liver showed fatty metamorphosis of slight degree. There was no arteriolar nephrosclerosis. The skeletal muscle fibers showed no abnormalities.

COMMENT

From a clinical standpoint it was clear that the patient in this case suffered from severe chronic myocardial insufficiency, but the cause of the heart failure was not apparent. Coronary arteriosclerosis without thrombosis or angina pectoris but with diffuse myocardial fibrosis could not be excluded and statistically is the most probable of the several possible causes of heart failure of obscure cause. The appearance of fever suggested the possibility of Fiedler's myocarditis, although it was realized that the elevated temperature could be due to pulmonary infarction.

The fatty degeneration discovered at autopsy was so severe, however, as to leave little doubt that it was the cause of the myocardial insufficiency. The muscle fibers were virtually full of fat, and there were severe degenerative changes involving the nuclei. The cause of this degeneration could not be ascertained. Such factors as inadequate diet, blood dyscrasias, chronic disease and infection could be eliminated. That the myocardial insufficiency itself could have produced such marked changes is contrary to all experience. Furthermore, such reasoning would leave one without an explanation as to why the heart failed in the first place.

CONCLUSION

Severe idiopathic fatty degeneration of the myocardium must be considered as an etiologic possibility in cases of heart failure of obscure origin.

DIABETES INSIPIDUS ASSOCIATED WITH DIABETES MELLITUS

METABOLIC STUDIES AND REPORT OF A CASE

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The development of glycosuria in a patient with diabetes insipidus is not unique and frequently accompanies this metabolic disorder.[1] The coexistence of frank diabetes mellitus and diabetes insipidus, on the other hand, is rare, and less than 25 case reports on patients with both dyscrasias [2] have been recorded in the available literature. Overlapping of signs and symptoms and the possible existence of at least two types of each disease have rendered the confirmation of both diagnoses difficult. Recent advances in the technic of study and interpretation of metabolic disorders have been of great help, however, and it is believed that the data to be presented satisfy the criteria for the diagnosis of diabetes insipidus and of diabetes mellitus.

The patient who will be discussed in this communication was under observation intermittently for more than eighteen months. On three occasions during this time she was admitted for observation to the

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Aided by the Corn Industries Research Foundation.

From the Medical Clinic of the Massachusetts General Hospital and the Fatigue Laboratory of Harvard University.

1. (*a*) Evans, G., and Wallis, R. L. M.: Diabetes Insipidus Complicated by Intermittent Glycosuria, Lancet **1**:70, 1921. (*b*) Rabinowitch, I. M.: Metabolic Studies on a Case of Diabetes Insipidus, Arch. Int. Med. **28**:355 (Sept.) 1921. (*c*) Gibson, R. G.; Magers, E. J., and Dulaney, H.: Blood Sugar Curves in Diabetes Insipidus and in Habitual and Experimental Excessive Water Drinking, Endocrinology **11**:341, 1927. (*d*) Lewin, C.: Zur Frage des Zusammenhangs des Diabetes mellitus und Diabetes insipidus, Med. Klin. **15**:133, 1919.

2. (*a*) Greene, J. A., and Gibson, R. B.: Coexistence of Diabetes Mellitus and Diabetes Insipidus: Report of a Case with Pregnancy, J. Lab. & Clin. Med. **24**:455, 1939. (*b*) Senator, H.: Ueber die Beziehungen zwischen Diabetes mellitus und insipidus, Deutsche med. Wchnschr. **24**:385, 1897. (*c*) Allan, F. N., and Rowntree, L. G.: The Association of Diabetes Insipidus and Diabetes Mellitus, Endocrinology **15**:97, 1931.

metabolism ward of the Massachusetts General Hospital. After the completion of certain routine procedures, an investigation of the constituents of body fluids, electrolyte exchange and renal function in the diabetes insipidus syndrome was pursued. No attempt will be made to survey the literature on diabetes insipidus. Several comprehensive reviews [3] have appeared in recent years, which do justice to the syndrome and its various manifestations.

METABOLIC REGIMEN AND LABORATORY METHODS

During most of her stay in the hospital the patient consumed a constant diet which contained 140 Gm. of carbohydrate, 62 Gm. of protein and 49 Gm. of fat. The difference between the weight of the freshly prepared diet and that of the same diet after desiccation was approximately 480 Gm. This refers to water in the food; it is not included in the columns on fluid intake in the tables. The intake of fluids was 4,000 cc. per day except when stated otherwise. Under this regimen the urine contained less than 0.1 Gm. of reducing substances daily. Preparation of the food, collection of excreta [4] and the methods used for analysis of the various constituents of the blood, the urine, the diet and the stool have been described.[5] Plasma volume was determined according to the method described by Gibson and Evans.[6] Interstitial fluid volume was determined according to the method of Crandall and Anderson.[7] Inulin and creatinine clearances were determined according to the method of Shannon and Smith.[8] Sodium, chloride and potassium clearances were calculated by the same formula as inulin clearance.

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3. (*a*) Peters, J. P.: Body Water: The Exchange of Fluids in Man, Springfield, Ill., Charles C. Thomas, Publisher, 1935. (*b*) Fisher, C.; Ingram, W. R., and Ranson, S. W.: Diabetes Insipidus and the Neuro-Hormonal Control of Water Balance, Ann Arbor, Mich., Edwards Brothers, Inc., 1938. (*c*) Bellows, R. T., and Van Wagenen, W. P.: The Relationship of Polydipsia and Polyuria in Diabetes Insipidus: A Study of Experimental Diabetes Insipidus in Dogs With and Without Esophageal Fistulae, J. Nerv. & Ment. Dis. **88**:417, 1938.

4. Talbott, J. H.; Jacobson, B. M., and Oberg, S. A.: The Electrolyte Balance in Acute Gout, J. Clin. Investigation **14**:411, 1935.

5. Talbott, J. H.: Interpretation of Clinical Chemical Procedures, Ohio State M. J. **35**:137, 1939.

6. Gibson, J. G., Jr., and Evans, W. A., Jr.: Clinical Studies of Blood Volume: I. Clinical Application of a Method Employing Azo Dye "Evans Blue" and the Spectrophotometer, J. Clin. Investigation **16**:301, 1937.

7. Crandall, L. A., Jr., and Anderson, M. X.: Estimation of the State of Hydration of the Body by the Amount of Water Available for the Solution of Sodium Thiocyanate, Am. J. Digest. Dis. & Nutrition **1**:126, 1934.

8. Shannon, J. A., and Smith, H. W.: The Excretion of Inulin, Xylose and Urea by Normal and Phlorizinized Man, J. Clin. Investigation **14**:393, 1935.

REPORT OF CASE

O. F., a white American-born housewife aged 46, was admitted to the Massachusetts General Hospital on Nov. 17, 1937, complaining of polyuria, polydipsia and pruritus vulvae.

Family History.—One sister was known to have diabetes mellitus. There were no other hereditary or congenital stigmas in the family.

Past History.—As a child the patient had intermittent severe headaches and nocturia (two to three times) each night. There was no history of trauma to the head or of any sickness which suggested encephalitis. During twenty-two years of married life she had been pregnant five times. She had three living children. The oldest child was treated for pulmonary tuberculosis in a sanatorium in 1929. Menstruation stopped at the age of 33, after the birth of her fifth child. Hot flashes appeared and persisted for more than a year. The early development of the menopause was not explained satisfactorily. In 1926 her weight was 230 pounds (104 Kg.). In 1936, it was 205 pounds (93 Kg.). On admission to the hospital it was 190 pounds (86 Kg.).

Present Illness.—The present illness began in 1932. Polyuria, polydipsia and severe headaches were the principal complaints. Medical advice was sought, and on a routine examination of the urine dextrose was found. A diagnosis of diabetes mellitus was made, and injections of insulin were recommended. These were taken daily for more than two years, with considerable subjective improvement. In 1934 the daily output of urine appeared to be increasing, and another physician was consulted. Examination of the urine at that time showed no reducing substances, while the low specific gravity suggested that another type of diabetes was present. The patient was advised to discontinue insulin, reduce her sodium chloride intake and take 1 cc. of solution of posterior pituitary U. S. P. parenterally daily. This advice was followed for more than two years, with partial alleviation of symptoms. In 1935 the location of her headaches changed from the top of her head to the temporal regions, and the incidence increased to at least once every twenty-four hours. Impairment of vision for near and distant objects was noted for the first time.

Two months before admission polydipsia and polyuria became more severe and a new symptom, pruritus vulvae, was noted. Glycosuria was rediscovered, and a determination of the value for "fasting blood sugar" showed the concentration to be 250 mg. per hundred cubic centimeters. She was referred to the hospital with the presumptive diagnosis of diabetes insipidus and diabetes mellitus.

Physical Examination.—Examination in the ward showed the patient to be well developed and moderately obese. The face was florid. All of the teeth had been removed. The vaginal mucous membrane was atrophied, and the uterus was slightly enlarged. The blood pressure was 150 systolic and 82 diastolic.

A neurologic examination by Dr. G. C. Caner gave negative results.

An examination of the eyes by Dr. E. B. Dunphy showed the visual acuity to be 20/40 in both eyes, with normal fundi and normal visual fields.

Partial Laboratory Data.—The specific gravity of the urine was 1.004. It contained about 0.1 per cent reducing substances but no albumin, ketone bodies, blood cells or casts. The Hinton reaction of the blood was negative. The concentration of serum cholesterol was 178 mg. per hundred cubic centimeters. An electrocardiogram was interpreted as normal. The roentgen ray films were interpreted by Dr. Richard Schatzski as follows: "Lateral and anterior-posterior views of the skull show slight elevation of the posterior clinoid processes without evidence of destruction. There is calcification of the dura near the longitudinal sinus.

The convoluted markings are increased. The findings are suggestive of a small tumor in the region of the pituitary body. The bones of the hands and feet appear normal."

A lumbar puncture showed normal dynamics. The fluid contained 19 mg. of protein per hundred cubic centimeters. No white or red blood cells were seen. The colloidal gold curve was 0000000000. The basal metabolic rate was determined on two occasions by the Tissot gasometer method. On December 9 it was + 9 per cent, and the respiratory quotient was 0.74. On December 21 it was — 1 per cent, and the respiratory quotient was 0.76. The rate of excretion of 6.0 mg. of phenolsulfonphthalein injected intravenously was 28 per cent in fifteen minutes and a total of 66 per cent in two hours. Other laboratory data are given in the tables.

Course.—Various experimental studies were done during each stay in the hospital. These will be discussed in detail. During the first stay an attempt was made to relieve the polydipsia, a most distressing symptom. Rinsing the mouth with cold water, sucking ice and a low sodium chloride intake proved to be effective. On the control diet, glycosuria was minimal and pruritus vulvae disappeared.

Readmission was advised for further study two months after discharge. The patient believed that her symptoms had improved in the interim. Thirst was less distressing, and it was necessary to void urine only once each night. The urine was tested for reducing substances several times a week. All tests gave negative results. She remained in the hospital one month.

The third admission occurred on Oct. 17, 1938. This was considered expedient in order to repeat certain experimental studies and to investigate the failing vision. The results of physical examination were unchanged except for the eyes, both of which showed cataracts. After completion of the experimental studies in the metabolism ward she was transferred to the Massachusetts Eye and Ear Infirmary, on November 30. Extraction of an intracapsular cataract from the left eye was successful, and recovery was uneventful.

Because of inability to control the severe headaches and the possibility of an expanding tumor of the pituitary a trial course of roentgen therapy was recommended. This consisted of 300 r daily to the region of the pituitary for six days. A 4 by 5 cm. field was used at a distance of 50 cm. Partial alleviation of headaches was achieved. The roentgen treatments were repeated, therefore, in May 1939. The same dosage, field and distance were employed. The patient was seen last in October. She believed that her general condition was better than at any time for more than three years. All of the previously distressing symptoms were alleviated. She continued with the same diet which had been prescribed at the first admission.

METABOLIC STUDIES

The data in support of a diagnosis of diabetes mellitus were convincing. The family history of diabetes mellitus, polyuria, polydipsia, glycosuria and pruritus vulvae, as well as the symptomatic relief after administration of insulin, was presumptive evidence. The sugar tolerance studies[9] confirmed this impression (table 1). The value for "fasting whole blood sugar" before each of three tests varied between 204 and 220 mg. per hundred cubic centimeters. An elevation of the level of blood sugar similar to that seen in patients with diabetes mellitus

9. Lindeboom, G. A.: Beobachtungen bei einem Fall von Diabetes insipidus et mellitus, Deutsches Arch. f. klin. Med. **175**:74, 1933.

followed ingestion of 100 Gm. each of dextrose, galactose and levulose. Two hours after ingestion of dextrose the concentration of blood sugar increased to 440 mg. per hundred cubic centimeters. The concentration of reducing substances in the urine collected at the same time was about 2.0 Gm. per hundred cubic centimeters. Ninety minutes after ingestion of galactose the concentration of blood sugar increased to 396 mg. per hundred cubic centimeters. Approximately 1.0 Gm. of reducing substances per hundred cubic centimeters was excreted in the urine. After the ingestion of levulose the concentration of blood sugar increased to a maximum of 276 mg. per hundred cubic centimeters. Acetone bodies in the urine were never observed by us. Since the prescribed diet in the hospital was sufficiently low in carbohydrate to prevent glycosuria, acetonuria from uncontrolled diabetes mellitus was not anticipated.

Our next interest was in confirmation of the diagnosis of diabetes insipidus and the study of several of its manifestations. Polydipsia, polyuria and headaches may be presenting symptoms of diabetes insipidus, as well as of diabetes mellitus. A low specific gravity of the urine and an increased concentration of serum sodium are significant laboratory findings. Presumptive exclusion of other dyscrasias completes the argument.

TABLE 1.—*Experimental Observations on Blood and Urine After Ingestion of 100 Gm. Each of Dextrose, Galactose and Levulose*

	Dextrose		Galactose		Levulose	
Time, Minutes	Blood Sugar, Mg. per 100 Cc.	Urine Sugar, Gm. per 100 Cc.	Blood Sugar, Mg. per 100 Cc.	Urine Sugar, Gm. per 100 Cc.	Blood Sugar, Mg. per 100 Cc.	Urine Sugar, Gm. per 100 Cc.
0	220	0.0	218	0.0	204	0.0
30	332	...	320	...	246	...
60	384	0.5	344	1.0	276	0.1
90	408	...	396	...	254	...
120	440	2.0	346	1.0	234	0.1
150	336	...	272	...	216	...
180	300	2.0	252	1.0	194	0.0

The daily water exchange varied from 4 to 8 liters. This is not excessive for a patient with diabetes insipidus and is less than that reported by some observers. Thirst, however, was persistent and insatiable. We believe that greater diagnostic significance should be given to the severity of thirst than to the absolute amount of fluid exchange. In cases of psychogenic polyuria, increased ingestion of fluid becomes habitual, and the output of urine may exceed 5 liters a day. Thirst is not insatiable, however, and restriction of fluids is not accompanied by distressing symptoms as it is in patients with diabetes insipidus.

A sustained low specific gravity of the urine is unusual in any disease except diabetes insipidus and advanced renal failure. Most routine specimens collected from this patient had a specific gravity below 1.006. The maximum specific gravity after thirty hours' abstinence from fluid was only 1.011. It was necessary to give solution of posterior pituitary [10] to increase the specific gravity above 1.020.

Appreciation of the significance of elevated values for serum sodium and total fixed base in diabetes insipidus is recent. It is believed, however, that they are of

10. Christie, C. D., and Stewart, G. N.: Study of a Case of Diabetes Insipidus with Special Reference to the Mechanism of the Diuresis and of the Action of the Pituitary Extract on It, Arch. Int. Med. **20**:10 (July) 1917.

great diagnostic help. About twenty years ago, Veil [11] and later Meyer and Meyer-Bisch [12] advanced the hypothesis that there are two kinds of diabetes insipidus, a hyperchloremic and a hypochloremic type. No satisfactory method for determination of the level of serum sodium was available at that time. It is likely that the terms "hypernatremic" and "hyponatremic" would have been used if sodium methods had been available, since the concentration of serum "sodium" is a better index of the concentration of sodium chloride than is the concentration of serum "chloride." Butler and his associates [13] were the first to study the increased concentration of serum sodium in diabetes insipidus and found that hyperchloremia is accompanied by hypernatremia.

The data in this communication confirm these observations. On the morning of Nov. 23, 1937, the concentration of serum sodium was 144.9 milliequivalents, and the concentration of total fixed base was 157.1 milliequivalents, per liter (table 2). These values are above the average range for normal persons (sodium, 139 to 141 milliequivalents, and total base, 150 to 155 milliequivalents, per liter) as determined in our laboratory.[5] It should be reiterated that during the week before this sample of blood was obtained the daily intake of fluid was 4,000 cc. This represented, probably, a restriction in the amount which would have been consumed had fluid been allowed ad libitum. The output of urine under this regimen was approximately 3,000 cc. daily. After collection of the first sample of blood the extradietary fluid intake was restricted to 100 cc. in twenty-four hours. All of the diet was consumed. In the twenty-four hour period the body weight diminished 1.8 Kg. The output of urine decreased 1,500 cc. Intense thirst was present, but chemical evidence of dehydration was lacking in the sample of blood taken on November 24. The oxygen capacity and cell volume had increased slightly, but the value for serum protein decreased from 6.8 to 6.5 Gm. per hundred cubic centimeters. The total fixed base, however, increased to 164.3 milliequivalents, that for sodium to 151.6 milliequivalents and that for chloride to 109.5 milliequivalents per liter, respectively. The increased concentrations of these constituents are believed to be significant and have been interpreted by us as confirmatory evidence of diabetes insipidus.

After relative abstinence from fluid for one day, amounts of 9,500 cc. and 7,500 cc. respectively were given in the subsequent twenty-four hour periods. The output of urine was 5,900 cc. for one period and 7,300 cc. for the other. A gain in weight of 0.8 Kg. was observed. A third sample of blood was taken on November 26. The concentrations of total fixed base, sodium and protein were similar to those observed in the first sample of blood. Thus it appeared possible to increase the concentrations of serum sodium by restriction of fluid, but depression of the concentration below normal was not achieved by ingestion of large amounts of fluid. In none of the samples of blood did the concentrations of potassium, calcium, phosphate or nonprotein nitrogen vary significantly from the average range for normal persons. There was some increase in the value for

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12. Meyer, E., and Meyer-Bisch, R.: Beitrag zur Lehre von Diabetes insipidus, Deutsches Arch. f. klin. Med. **137**:225, 1921.

13. Butler, A. M.; Harper, E. A., and Carey, B. W., Jr.: Excretion of Sodium and Chloride in Normal Persons and in Patients with Nephritis and Diabetes Insipidus, Am. J. Dis. Child. **46**:1459 (Dec.) 1933.

Date	Time, A.M.	Whole Blood: Oxygen Capacity, mM per Liter	Whole Blood: Cell Volume, Per Cent	Serum: p_H	Serum: Total Fixed Base, mEq. per Liter	Serum: Sodium, mEq. per Liter	Serum: Potassium, mEq. per Liter	Serum: Calcium, mEq. per Liter	Serum: Total CO_2, mM per Liter	Serum: Chloride, mEq. per Liter	Serum: Phosphate, mEq. per Liter	Serum: Protein, Gm. per 100 Cc.	Cells: Non-protein Nitrogen, Mg. per 100 Cc.	Cells: Chloride, mEq. per Liter	Cells: Water, Gm. per Liter	Chloride Ratio	Comment
11/23/37	8	8.86	44.3	....	157.1	144.9	4.3	4.9	31.0	104.7	2.2	6.8	28	....	...	....	Mild thirst
11/24/37	8	9.84	46.7	....	164.3	151.5	4.3	4.9	33.5	109.5	2.7	6.5	29	....	...	....	Intense thirst
11/26/37	8	9.34	45.1	....	157.1	144.7	4.1	4.8	30.4	106.3	2.3	6.9	25	....	...	....	Mild thirst
12/14/37	8	....	45.4	....	155.7	143.3	3.9	4.8	27.3	104.7	2.3	6.6	21	....	...	....	Mild thirst
12/17/37	8	9.43	44.2	7.39	159.2	146.2	3.8	4.8	27.0	108.2	2.4	6.6	29	....	...	....	Moderate thirst
12/18/37	8	9.40	44.9	7.42	162.1	148.7	3.9	5.0	26.0	111.2	2.3	6.9	25	....	...	....	Moderate thirst
12/22/37	8	9.11	41.2	....	167.7	153.9	3.4	4.9	32.0	115.1	2.5	6.4	22	....	...	....	Intense thirst
3/21/38	11	....	40.6	....	161.8	149.0	...	...	....	.....	...	6.4	..	....	...	....	Moderate thirst
3/24/38	8	....	43.3	....	164.7	152.9	4.0	...	....	111.4	...	6.9	43	....	...	....	Intense thirst
3/24/38	11	....	42.5	....	164.7	.....	...	...	....	.....	...	6.7	..	....	...	....	Intense thirst
3/31/38	8	....	38.4	....	163.2	150.5	3.6	...	....	112.1	...	6.0	..	....	...	....	Intense thirst
3/31/38	11	....	37.3	....	164.1	.....	...	...	....	.....	...	5.7	18	....	...	....	Intense thirst
4/ 6/38	8	....	38.9	....	152.3	142.5	3.6	...	....	101.6	...	6.4	23	....	...	....	Mild thirst
4/ 6/38	11	....	36.6	....	157.1	.....	3.6	...	....	.....	...	6.1	22	....	...	....	Mild thirst
10/22/38	8	....	46.3	....	156.8	142.5	4.0	4.9	26.5	104.5	...	7.1	34	....	...	....	Mild thirst
10/29/38	8	....	41.1	....	153.4	142.0	4.0	4.9	28.0	100.7	...	6.9	33	....	...	....	Mild thirst
11/ 7/38	8	....	42.8	....	156.5	145.4	4.5	5.0	26.9	106.7	...	6.9	29	45.2	715	0.55	Moderate thirst
11/ 9/38	8	....	38.0	....	161.4	150.5	4.3	4.9	27.5	113.7	...	6.1	28	51.7	713	0.65	Intense thirst
11/22/38	8	....	36.8	....	158.4	144.5	4.9	...	17.5	117.4	...	5.9	..	61.9	724	0.68	Mild thirst
11/29/38	8	....	33.6	....	161.2	149.9	3.4	...	36.0	101.2	...	5.8	32	46.1	712	0.60	Mild thirst

TABLE 3.—*Body Weight, Fluid Intake and Data on Urine*

Period	Date	Body Weight, Kg.	Fluid Intake, Cc.	Urine: Volume, Cc.	Urine: p_H	Urine: Specific Gravity	Urine: Ammonia N., mEq.	Urine: Sodium, mEq.	Urine: Potassium, mEq.	Urine: Calcium, mEq.	Urine: Magnesium, mEq.	Titratable Acid at p_H of 7.4, mEq.	Phosphate at p_H of 7.4: Chloride, mEq.	Phosphate at p_H of 7.4, mEq.	Total Nitrogen, Gm.
I	12/14-15/37.....	76.5	4,000	4,690	6.7	1.003	44.5	35.4	38.4	9.1	0.4	22.0	41.4	25.4	9.6
	12/15-16/37.....	76.7	4,000	4,600	6.0	1.003	37.5	33.3	29.0	11.8	1.7	19.5	39.3	21.7	8.7
	12/16-17/37.....	76.6	4,000	4,830	6.1	1.003	35.0	34.5	31.7	10.5	4.5	23.0	41.4	22.1	8.9
II	12/17-18/37.....	76.7	180	2,630	5.8	*	35.0	39.4	37.3	10.1	5.9	24.0	49.3	21.8	8.7
	12/18-19/37.....	76.1	4,000	3,940	6.0	1.003	36.0	53.3	31.3	8.7	4.8	20.5	56.1	18.1	8.6
	12/19-20/37.....	76.6	4,000	4,180	6.0	1.004	34.5	52.5	36.5	12.6	5.5	20.5	60.2	20.4	8.7
III	12/20-21/37.....	76.1	4,000	3,630	6.4	1.006	32.5	174.8	65.6	9.9	5.3	18.5	195.0	26.3	8.8
	12/21-22/37.....	76.2	4,000	3,870	6.3	1.007	40.5	330.5	65.6	11.3	5.9	15.5	361.0	23.0	8.6
	12/22-23/37.....	75.9	4,000	3,930	6.3	1.005	35.5	186.0	40.2	9.6	4.1	15.0	191.5	18.3	9.0
	12/23-24/37.....	75.5	4,000	4,420	6.7	1.005	35.0	129.0	36.7	11.9	4.8	12.0	123.3	24.7	9.3
IV	10/25-26/38.....	69.1	4,000	3,680	5.9	.....	41.1	10.2	41.2	9.9	6.4	27.2	18.8	....	12.1
	10/26-27/38.....	69.1	4,000	3,540	5.9	.....	40.7	9.2	46.7	9.7	6.2	26.4	16.1	....	12.3
	10/27-28/38.....	69.2	4,000	3,770	5.9	.....	39.5	9.3	45.5	9.8	6.0	25.6	15.1	....	12.4
	10/28-29/38.....	69.0	4,000	3,650	5.9	.....	37.7	8.5	45.5	8.9	4.8	28.8	12.3	....	12.1
V	11/ 7- 8/38.....	69.1	4,000	3,200	6.3	.....	32.8	111.4	51.8	9.7	6.0	22.8	116.4	....	10.5
	11/ 8- 9/38.....	69.9	4,000	3,440	6.4	.....	37.2	240.1	59.6	11.1	6.0	20.4	256.0	....	9.3
	11/ 9-10/38.....	70.6	4,000	4,560	6.7	.....	35.6	163.2	43.9	12.7	7.1	15.5	160.5	....	10.3
	11/10-11/38.....	69.8	4,000	4,190	6.8	.....	28.9	101.8	42.9	10.1	4.6	15.1	88.8	....	9.9

* Specimens were partitioned and a maximum specific gravity of 1.011 was observed between 4:30 and 5:40 a. m.

total carbon dioxide during the first stay in the hospital. This was not observed subsequently except after ingestion of sodium bicarbonate.

Three weeks later these experiments were repeated, and collections of excreta were made. The first period (table 3) extended from December 14 to December 17. The fluid intake was maintained at 4,000 cc. daily. The second period began December 17. The fluid intake on the first day was 180 cc.; on the second and third day it was 4,000 cc. The third period lasted from December 20 to 24. The experimental conditions were similar to those of the first period, except that 20 Gm. of sodium chloride was ingested daily on the first two days. The blood pressure in millimeters of mercury before ingestion of salt was 124 systolic and 88 diastolic. After the two days of salt ingestion it was 168 systolic and 108 diastolic. In each period an aliquot sample of one day's diet was dried and prepared for analysis of various constituents.

Samples of blood were taken on December 14, 17, 18 and 22. On December 17 there was an increase in concentration of total fixed base, sodium and chloride over the values observed on December 14. This is interpreted as evidence that the fluid requirements at this time were in excess of the 4,000 cc. allowed daily. After twenty-four hours of rigid restriction of fluids the concentrations of sodium and chloride were similar to those observed in the previous dehydration experiment. The highest concentrations of serum sodium and chloride were observed after the ingestion of sodium chloride. The concentration of sodium was 153.9 milliequivalents and that of chloride 115.1 milliequivalents per liter. There was an increase of about 5 millimols per liter in concentration of serum carbon dioxide as compared with a maximum increase of 2.5 millimols in the dehydration experiments. As in the first experiments, minimal changes were observed in the concentrations of potassium, calcium, phosphate, protein and nonprotein nitrogen.

The data on intake and output are summarized in table 4. The "balance observations" for potassium, magnesium, phosphate and total nitrogen show that equilibrium was achieved for these substances. The body was not in equilibrium, however, in the exchange of calcium, sodium and chloride. A negative calcium balance was observed but not explained. Although the patient was confined to the metabolism ward, she was ambulatory, and it is doubtful if this imbalance can be attributed to inactivity. Roentgenograms of the skeleton showed no generalized decalcification, and it is presumed that the dissipation of calcium either was transient or had persisted for only a short time. An appreciable retention of sodium and chloride was observed in each period. The amount retained was dependent on intake and was greater during the period when extradietary salt was given.

The patient was admitted the second time for study of body fluid volumes (table 5) as well as for further study of serum electrolytes. On March 21, 750 cc. of fluid was given between 7 and 7:30 a. m. At 8 a. m. Evans' blue dye (T-1824, Eastman Kodak Co.) and sodium thiocyanate were injected for determination of plasma volume and interstitial fluid volume. No further water was allowed until the experiment was finished. No symptoms of thirst were noticed during the determination of plasma volume. Moderate thirst developed before completion of the interstitial fluid volume experiment, at 11:30 a. m. These observations were used as controls for subsequent experiments.

The studies were repeated on March 24. One hundred and twenty cubic centimeters of extradietary water and the control diet were the only ingesta allowed in the thirty hours previous to the experiment. The volume of urine passed in the twenty-four hour period before the beginning of the experiment was 1,260 cc.

TABLE 4.—*Summary of Certain Balance Data*

	Sodium, mEq.	Potassium, mEq.	Calcium, mEq.	Magnesium, mEq.	Chloride, mEq.	Phosphate, mEq.	Total Nitrogen, Gm.
First Period, Dec. 14 to 17, 1937							
Dietary intake	227	164	47	47	227	77	33
Urinary output	102	99	31	7	122	69	27
Fecal output	33	66	94	31	13	31	5
Daily balance	+30.6	— 0.4	—26.0	+ 3.4	+30.6	— 8.0	+ 0.4
Second Period, Dec. 17 to 20, 1937							
Dietary intake	227	151	47	44	216	73	34
Urinary output	145	105	31	18	166	60	26
Fecal output	21	33	45	20	7	20	3
Daily balance	+19.0	+ 4.3	— 9.8	+ 2.1	+14.4	— 2.3	+ 1.5
Third Period, Dec. 20 to 24, 1937							
Dietary intake	328	232	189	55	276	92	43
Extradietary intake	684	...	...	...	684	...	...
Urinary output	830	208	43	20	871	92	36
Fecal output	35	46	178	26	15	29	6
Daily balance	+38.8	— 5.6	— 7.8	+ 2.2	+18.6	— 7.5	+ 0.4
Fourth Period, Oct. 25 to 29, 1938							
Dietary intake	120	287	55	...	95	118	54
Extradietary intake	...	...	...	...	...	...	...
Urinary output	37	179	38	...	62	101	49
Fecal output	30.0	83.0	30.6	...	16.5	28	5.7
Daily balance	+13.2	+ 6.2	— 3.5	....	+ 4.0	— 2.7	— 0.2
Fifth Period, Nov. 7 to 11, 1938							
Dietary intake	136	279	48	...	100	119	50
Extradietary intake	684	...	...	...	684	...	...
Urinary output	517	198	44	...	621	92	40
Fecal output	38.3	47.6	39.4	....	12.1	29	3.8
Daily balance	+66.2	+ 8.3	— 8.7	...	+37.6	— 0.5	+ 1.5

TABLE 5.—*Experimental Observations on Volume of Body Fluids*

Date, 1938	Plasma Volume, Cc.	Interstitial Fluid	
		Liters	Per Cent of Body Weight
March 21	2,580	15.5	20.8
March 24	2,450	15.0	20.4
March 31	2,740	15.7	21.5
April 6	2,800	16.7	23.4
October 29	2,580	15.2	22.1
November 22	3,440	15.4	22.5
November 29	3,440	....	....

The body weight decreased 1.4 Kg. Symptoms of thirst were noted shortly after the beginning of abstinence from fluid and became intense before the end of the period. The buccal mucous membrane appeared to be very dry. The plasma and interstitial fluid volumes as determined during intense thirst showed only slight variation from those observed when thirst was less distressing. Plasma volume showed a maximum decrease of 130 cc., or 5 per cent, and interstitial fluid volume a decrease of 500 cc., or 3 per cent.

On each of the three consecutive days beginning March 28, 20 Gm. of sodium chloride was given by mouth. The fluid intake was maintained at 4,000 cc. The volume studies were repeated March 31. Symptoms of thirst appeared to be as intense as during the dehydration experiment. The changes in body fluid volumes, however, were the reverse of those observed previously. The plasma volume increased 14 per cent, and the interstitial fluid volume increased 4 per cent. The value for serum base remained elevated, while that for serum protein decreased to 5.9 per cent; evidently the serum was diluted with slightly hypertonic physiologic solution of sodium chloride.

A control experiment was repeated on April 6. One thousand cubic centimeters of water was ingested thirty minutes before the test. During the test, thirst was slight. The plasma volume was 2,800 cc., the maximum observed in any experiment. The interstitial fluid volume was 16.7 Kg. This was 10 per cent greater than during the first experiment. The concentrations of total base, sodium and chloride in the serum were in the normal range.

Inulin and creatinine clearances (table 6) were determined on April 1. During three collection periods, the average inulin clearance was 93 cc. per minute and the creatinine clearance was 139 cc. per minute. These are considered as normal values. On April 11 these studies were repeated after injection of 0.5 cc. of solution of posterior pituitary U. S. P. The creatinine clearance showed little change, while the inulin clearance increased 13 per cent, to 105 cc. per minute.

The plasma and interstitial fluid volumes were determined on October 29 under conditions similar to those on March 21. The observations checked satisfactorily. On November 22 the volume studies were repeated. During the thirty-six hours before this test, 18 Gm. of ammonium chloride was ingested. A daily intake of 4,000 cc. of water was maintained. The patient denied having distressing symptoms of thirst during the test. The plasma volume increased 860 cc., or 33 per cent. No change was observed in the interstitial fluid volume. The values for serum sodium and total base were only slightly above normal. The value for serum chloride, however, was 117.5 milliequivalents per liter, and that for total carbon dioxide in the serum was 17.5 millimols per liter. This is indicative of severe chloride acidosis. One week later 40 Gm. of sodium bicarbonate was given, and the tests were repeated. Minimal symptoms of thirst were present. The body weight increased 1.4 Kg. with ingestion of alkali. The plasma volume remained unchanged. The determination of interstitial fluid volume was unsatisfactory owing to technical difficulties. The concentration of serum sodium was increased to 149.9 milliequivalents per liter. The value for serum chloride was 101.2 milliequivalents, and that for total carbon dioxide in the serum was 36 millimols, per liter.

The clearance tests for inulin, creatinine, sodium, chloride and potassium were repeated on three separate days. From October 29 to November 1 the total sodium chloride intake was restricted to 1.5 Gm. daily. Observations on renal clearance were made on November 1. The clearances of inulin and creatinine were similar to those of April 1. The clearances of sodium and chloride, how-

TABLE 6.—*Experimental Observations on Renal Clearance*

Date, 1938	Time, A.M.	Urine Flow, Cc. per Minute	Inulin		Creatinine Cc. Plasma Cleared per Minute	Creatinine-Inulin Ratio	Sodium, Cc. Plasma Cleared per Minute	Chloride, Cc. Plasma Cleared per Minute	Potassium, Cc. Plasma Cleared per Minute	Specific Gravity of Urine	Blood Pressure	Comment
			Cc. Plasma Cleared per Minute	Urine-Plasma Ratio								
April 1.....	9:48-10.00	12.2	100	8.2	137	1.37	....	....	....	1.009	.....	
	10:00-10:24	11.0	91	8.2	137	1.51	....	....	....	1.007	.....	
	10:24-10:35	10.8	87	8.1	144	1.67	....	....	....	1.005	.....	
April 12*.....	9:13- 9:26	2.46	115	46.5	124	1.09	....	....	....	1.030	136/86†	0.5 cc. solution of posterior pituitary U. S. P. given hypodermically at 7 a. m.
	9:26- 9:37	2.91	107	36.7	131	1.23	....	....	....	1.018	120/84	
	9:37- 9:50	2.49	93	37.5	125	1.35	....	....	....	1.014	120/80	
November 1....	9:31- 9:41	9.6	78	8.1	119	1.53	0.15	0.52	8.2	.....	.....	Preceded by a low salt diet for 3 days
	9:41- 9:51	10.4	86	8.1	128	1.49	0.19	0.56	8.8	.....	.....	
	9:51-10:01	12.4	101	8.1	150	1.48	0.21	0.64	10.6	.....	.....	
November 11...	9:34- 9:44	9.4	76	8.1	137	1.80	2.10	....	8.0	.....	.....	Preceded by a high salt diet for 3 days
	9:44- 9:54	11.0	88	8.0	132	1.50	3.40	....	9.2	.....	.....	
	9:54-10:04	10.3	105	10.2	159	1.51	3.50	....	12.5	.....	.....	
November 19§..	9:12- 9:22	2.6	122	46.8	192	1.57	1.20	1.29	8.6	.....	.....	0.5 cc. solution of posterior pituitary U. S. P. given hypodermically at 6:45 a. m.
	9:22- 9:42	2.8	135	48.6	167	1.24	1.00	1.64	7.9	.....	.....	

* The urine flow following injection of solution of posterior pituitary was 18 cc. from 7 to 8 a. m. and 74 cc. from 8 to 9:13 a. m.
† The blood pressure at 7 a. m. was 124/70 and at 8:50 a. m. was 140/88.
§ The urine flow following injection of solution of posterior pituitary was 48 cc. from 7 to 8 a. m. and 82 cc. from 8 to 9:12 a. m.

ever, which were determined for the first time in this case, were considerably less than the average range for normal persons. In a study of 10 patients with various disorders but with normal ability to clear plasma of inulin (95 cc. or more per minute) the average rate of sodium clearance was 1.60 cc. per minute and that of chloride clearance 2.47 cc. per minute.[14] After restriction of sodium chloride the patient under discussion showed a sodium clearance of 0.18 cc. of plasma per minute and a chloride clearance of 0.58 cc. of plasma per minute. After a high sodium chloride intake (20 Gm. of sodium chloride per day for two days and 8 Gm. on the morning before beginning the test) the clearances were redetermined. Inulin and creatinine clearances were unchanged from the previous observations. Sodium clearance increased more than tenfold. Samples for chloride concentration were destroyed inadvertently. The last series of clearance tests was done on November 19. Shortly before the test, 0.5 cc. of solution of posterior pituitary U. S. P. was given. Reduction in the flow of urine was apparent, with an elevated clearance of all of the constituents determined except potassium. The sodium clearance was equivalent to 1.10 cc. of plasma cleared per minute, and the chloride clearance, to about 1.80 cc. per minute. The values for potassium clearance were similar in the 3 experiments.

COMMENT

All of the criteria necessary for a diagnosis of diabetes mellitus were satisfied. The development of diabetes mellitus in a sister of the patient is significant. The symptoms—polyuria, polydipsia, pruritus vulvae and loss of weight—are characteristic. Glycosuria and a diabetic type of blood sugar response following ingestion of 100 Gm. each of three sugars confirm the presumptive diagnosis. Symptomatic relief after insulin treatment and, later, after moderate restriction of carbohydrate consumption is additional evidence.

Equally adequate data were obtained to substantiate a diagnosis of diabetes insipidus. Intense thirst was persistent through the day and wakened the patient intermittently at night. When fluid was allowed ad libitum, the daily intake varied between 5 and 8 liters. When fluids were forced, satiation was not achieved until more than 10 liters had been consumed. Other causes of persistent polydipsia and polyuria, such as Bright's disease and emotional polydipsia, were considered to be unlikely. Also, agents or syndromes which produce symptomatic diabetes insipidus,[15] such as trauma to the hypothalmus, encephalitis, syphilis of the central nervous system and xanthomatosis, were believed to have been excluded.

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14. Talbott, J. H.; Coombs, F. S.; Consolazio, W. V., and Pecora, L. J.: Unpublished data.

15. (*a*) Weir, J. F.; Larson, E. E., and Rowntree, L. G.: Studies in Diabetes Insipidus, Water Balance and Water Intoxication: Study I, Arch. Int. Med. **29**:306 (March) 1922. (*b*) Warkany, J., and Mitchell, A. G.: Diabetes Insipidus in Children: A Critical Review of Etiology, Diagnosis and Treatment, with Report of Four Cases, Am. J. Dis. Child. **57**:603 (March) 1939.

The urine passed was of low specific gravity, usually 1.003 to 1.006. The maximum value observed during dehydration was 1.011. After injection of solution of posterior pituitary the maximum was 1.030. The abnormally high concentrations of sodium and chloride in the serum are interpreted as further evidence in support of a diagnosis of diabetes insipidus. The value for serum sodium usually was high normal or above normal. Maximum concentrations were observed after abstinence from fluid for thirty hours and after ingestion of large amounts of sodium chloride. During an elapsed time of more than a year, the value for serum sodium varied between 142 and 150 milliequivalents per liter at twelve determinations. It was greater than 150 milliequivalents per liter at five determinations. The changes in the concentration of sodium were accompanied by a molar equivalent increase in that of total fixed base. The concentration of serum chloride was increased less constantly than that of sodium. In only six of the samples was it greater than 110 milliequivalents per liter. These changes are the basis for the statement made previously that this type of diabetes insipidus should be termed "hypernatremic" rather than "hyperchloremic."

Butler and his associates [15] have reported concentrations of the same magnitude in 1 patient with diabetes insipidus. Peters,[3a] in a summary of the literature, concluded that there are no characteristic changes in the concentration of constituents of the blood, although he referred to 1 patient [16] in whose case a serum sodium concentration of 147.2 milliequivalents per liter was recorded. We prefer to attach considerable significance to an elevation of this magnitude. In normal persons some increase in the values for serum sodium and total base may accompany ingestion of large amounts of sodium chloride.[17] Concentrations similar to those observed in this patient, however, are seen only in dyscrasias associated with a profound disturbance of the acid-base balance of the body.

It is important to emphasize that the increased concentration of serum sodium was achieved with minimal variations in serum protein, calcium and potassium and in cell volume. The syndrome does not have, therefore, the characteristics of dehydration with which one is accustomed to associate excessive loss of fluid from the body.

The pathogenesis in human beings of diabetes mellitus as well as of diabetes insipidus remains to be defined. In experimental animals, von Mering and Minkowski showed that surgical removal of the pancreas produced a disease which resembled diabetes mellitus. The

16. Lavietes, P. H.; D'Esopo, L. M., and Harrison, H. E.: The Water and Base Balance of the Body, J. Clin. Investigation **14**:251, 1935.

17. Loeb, R. F.; Atchley, D. W.; Richards, D. W., Jr.; Benedict, E. M., and Driscoll, M. E.: On the Mechanism of Nephrotic Edema, J. Clin. Investigation **11**:621, 1932.

anatomic changes in the pancreas which have been observed at necropsy in patients with clinical diabetes, however, are disappointing. Recently, Houssay [18] and Long [19] have noted that the development of so-called pancreatic diabetes may be prevented by hypophysectomy. These experiments gave rise to the hypothesis that sugar diabetes is related to a hypersecretion of the diabetogenic hormone from the anterior lobe of the pituitary. Young [20] was the first who was successful in producing hyperglycemia in animals by injection of pituitary extracts. While these observations are pertinent to our argument, it is not believed to be proved that the common variety of clinical diabetes mellitus is dependent on hyperfunctioning cells of the anterior lobe of the hypophysis.

The pathogenesis of human diabetes insipidus is equally uncertain. Fisher, Ingram and Ransom [3b] have produced permanent polyuria in animals by interruption of the nervous pathway from the nucleus supraopticus to the hypophysis, with atrophy of the pars nervosa. These changes were thought to be accompanied by a decreased elaboration of the antidiuretic, pressor and oxytocic substances. In human beings as well as in animals, surgical removal of the whole pituitary gland or destruction by massive tumors with interruption of the supraopticohypophysial tract does not result in permanent diabetes insipidus. There is, therefore, anatomic evidence which suggests that clinical diabetes insipidus is dependent on a functioning anterior lobe [21] as well as interruption of certain pathways to the posterior lobe. Beyond this there is little concurring evidence.

In the patient under consideration we should like to believe that the two types of diabetes have a related pathogenesis.[22] Increased elaboration of the diabetogenic hormone from hyperplasia of the cells of the anterior lobe of the pituitary with secondary effects from pressure on the supraopticohypophysial tract constitutes a satisfactory working hypothesis.

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18. Houssay, B. A.: Carbohydrate Metabolism, New England J. Med. **214**: 971, 1936.

19. Long, C. N. H.: The Influence of the Pituitary and Adrenal Glands upon Pancreatic Diabetes, Medicine **16**:215, 1937.

20. Young, F. G.: Experimental Investigations on Relationship of Anterior Hypophysis to Diabetes Mellitus, Proc. Roy. Soc. Med. **31**:1305, 1938.

21. von Hann, F. V.: Ueber die Bedeutung der Hypophysenveränderungen bei Diabetes insipidus, Frankfurt. Ztschr. f. Path. **21**:337, 1918. Richter, C. P.: Experimental Diabetes Insipidus: Its Relationship to the Anterior and Posterior Lobes of the Hypophysis, Am. J. Physiol. **110**:439, 1934.

22. Gellerstedt, N., and Grill, C.: A Clinical and Anatomic Contribution to the Knowledge of Combined Diabetes Mellitus and Insipidus: Report of a Case Treated with Insulin and Salyrgan in Which the Patient Died with Symptoms of Hypoglycemia, Acta med. Scandinav. **75**:586, 1931. Steel, R. S.: Diabetes and Dyspituitarism, Proc. Staff Meet., Mayo Clin. **2**:216, 1927. Greene and Gibson.[2a]

The incidence of glycosuria, hyperglycemia and even frank diabetes mellitus in patients with pituitary tumors of various types speaks for the explanation.[23] The chronologic order of development of symptoms supports the hypothesis. Convincing arguments against this explanation are the infrequent occurrence of polyuria in patients with a pituitary tumor and the resistance to insulin [24] frequently observed in such syndromes.

The participation of other endocrine glands in the syndrome was not apparent. The basal metabolic rate was within the normal range at two examinations. Menstruation had not been observed for fourteen years, but the presence of hot flashes during the menopause indicated primary gonadal hypofunction and not hypofunction secondary to a pituitary lesion.

The data on balance (tables 2, 3 and 4) show a retention of sodium and chloride in each of the five periods. Similar findings have been reported by Peters [3a] and Weir [25] in studies on patients with diabetes insipidus receiving a high sodium chloride intake. In our patient the positive balance was accompanied by an increased concentration of these constituents in the serum. The body weight and body fluid volumes showed little change during the respective periods of observation. The retention of sodium and chloride, then, must have been achieved by an increase in concentration in body fluids without a concomitant retention of water. The observations fail to substantiate the hypothesis of Stehle [26] that the polyuria of diabetes insipidus is a salt diuresis from inability of the tissues to retain salt. In this syndrome the tissues retain salt with ease; to relinquish it is difficult.

Retention of sodium chloride without retention of water is encountered infrequently in experimental medicine. The mechanism may be attributed either to a quantitative diminution in rate of filtration of plasma through the renal glomeruli or to increased reabsorption of sodium chloride by the tubules. The values for inulin clearance in this case showed a normal filtration rate. This agrees with the observations made on creatinine clearance by Butler and his associates.[13] If a normal filtration rate is accepted, then increased tubular reabsorption must be considered in any attempt to explain the phenomenon. Threshold sub-

23. Cushing, H.: The Basophil Adenomas of the Pituitary Body and Their Clinical Manifestations (Pituitary Basophilism), Bull. Johns Hopkins Hosp. **50**: 137, 1932.

24. Davidoff, L. M., and Cushing, H.: Studies in Acromegaly: VI. The Disturbance of Carbohydrate Metabolism, Arch. Int. Med. **39**:751 (June) 1927.

25. Weir, J. F.: Observations on the Influence of Pituitary Extract on the Metabolism in Diabetes Insipidus, Arch. Int. Med. **32**:617 (Oct.) 1923.

26. Stehle, R. L.: The Diuretic-Antidiuretic Action of Pituitary Extract, Am. J. Physiol. **79**:289, 1927.

stances, such as sodium and chloride, should show a diminished clearance if tubular reabsorption is increased above normal. The data confirm this presumption. Sodium and chloride clearances on Nov. 1, 1938 were well below normal. On November 19, injection of solution of posterior pituitary caused an increase in clearance rates, but normal values were not achieved. A high sodium chloride intake (November 11) proved the only effective means of increasing the clearance rates of the respective substances above normal. Increased reabsorption of sodium chloride, therefore, is believed to be an important pathogenic mechanism in the production of diabetes insipidus. This action is essentially the opposite of that in adrenal insufficiency, a condition associated with decreased tubular reabsorption of sodium and chloride.[27]

Inspection of the data reveals that the retention of electrolytes and disturbance of renal clearance were confined to sodium and chloride. The values for potassium, calcium and phosphate clearance were normal. It is important for our argument to stress the point that approximate nitrogen equilibrium was achieved during each experimental period. The changing state applied only to sodium and chloride.

The filtration rate as measured by inulin clearance was increased slightly after injection of solution of posterior pituitary. This does not agree precisely with the study of Burgess, Harvey and Marshall [28] who observed no increase in xylose clearance in dogs under similar conditions. Since some xylose is reabsorbed by the renal tubules, the experiments are not strictly comparable. Our observations suggest that posterior pituitary has a diuretic [29] action, i. e., an increase in glomerular filtration. This is ineffective, however, because the principal action is antidiuretic, i. e., reabsorption of water by the tubules.

In concluding the discussion of renal function in patients with diabetes insipidus, attention should be called to the changing clearances in consecutive ten minute periods. Many clearance determinations have been made by us during the past three years for patients with normal and pathologic kidneys. With the technic employed, inulin and creatinine values for other patients have been remarkably constant during consecutive collection periods.[30] It is believed that the results in this

27. Gersh, I., and Grollman, A.: Kidney Function in Adrenal Cortical Insufficiency, Am. J. Physiol. **125**:66, 1939.

28. Burgess, W. W.; Harvey, A. M., and Marshall, E. K., Jr.: The Site of the Antidiuretic Action of Pituitary Extract, J. Pharmacol. & Exper. Therap. **49**:237, 1933.

29. Bourquin, H.: Studies on Diabetes Insipidus: II. The Diuretic Substance; Preliminary Observations, Am. J. Physiol. **83**:125, 1927.

30. Smith, H. W.: The Physiology of the Kidney, New York, Oxford University Press, 1937.

patient should not be attributed to technical errors. Continuously changing renal function seems to us to be a more acceptable explanation.

An interesting by-product of this investigation were the conclusions concerning the mechanism of thirst. Thirst apparently is insatiable in cases of untreated diabetes insipidus and as a symptom has received considerable attention in this syndrome. Conclusions derived from this and similar studies may not be utilized directly to augment understanding of thirst in normal persons. Certain implications, however, are noteworthy and may be significant. Changes in plasma volume, interstitial fluid volume and concentrations of sodium chloride in the blood, individually or in association, have been thought to be important in the pathogenesis of thirst. Weir and his associates [15a] observed normal blood and plasma volumes in patients with diabetes insipidus. No change in volumes after injection of solution of posterior pituitary was observed. Our data, which comprise, in addition, records of interstitial fluid volume are in agreement. Only small changes in body fluid volumes followed abstinence from fluid or ingestion of sodium chloride, although thirst, which accompanied many of the experimental procedures, was intense.

It may be argued that the increased concentrations of serum sodium and chloride were responsible for the intense symptoms. An increased concentration of either sodium or chloride without concomitant elevation of the other will not produce intense thirst. Thus, on Nov. 22, 1938, the concentration of serum chloride was 117.4 milliequivalents, and that of serum sodium, 144.5 milliequivalents, per liter. The volume of plasma was increased, and thirst was minimal. One week later the concentration of serum sodium was 149.9 milliequivalents and that of serum chloride 101.2 milliequivalents per liter, and the plasma volume was 3,440 cc. Again, thirst was minimal. The hypothesis of Arden [31] that thirst is governed by sodium alone was not confirmed by these experiments.

The conclusion seems inescapable that, just as respiration is controlled by several factors,[32] so thirst is controlled by several factors.[33] Dryness of the mouth as a local process [34] or as a result of general depletion of body water [35] may account for thirst at times. An increased

31. Arden, F.: Experimental Observations upon Thirst and on Potassium Overdosage, Australian J. Exper. Biol. & M. Sc. **12**:121, 1934.

32. Henderson, L. J.: Blood: A Study in General Physiology, New Haven, Conn., Yale University Press, 1928.

33. Dill, D. B.: Life, Heat and Altitude: Physiological Effects of Hot Climates and Great Heights, Cambridge, Mass., Harvard University Press, 1938.

34. Cannon, W. B.: The Physiological Basis of Thirst: Croonian Lecture, Proc. Roy. Soc., London, s.B **90**:283, 1918.

35. Gregersen, M. I., and Cannon, W. B.: Studies on the Regulation of Water Intake: I. The Effect of Extirpation of the Salivary Glands on the Water Intake of Dogs While Panting, Am. J. Physiol. **102**:336, 1932.

concentration of serum sodium and chloride without depletion of plasma or interstitial fluid volume and without reduction of water in the blood cells appears to be important at other times.

SUMMARY AND CONCLUSIONS

Metabolic studies on a patient with diabetes mellitus and diabetes insipidus are described. The clinical diagnosis of both dyscrasias appeared to be confirmed by the laboratory data. In an attempt to explain both endocrine dysfunctions by a single lesion, it was suggested that a hyperplastic and hyperfunctioning anterior pituitary lobe might have encroached on the supraopticohypophysial pathway. A presumption of pituitary tumor was substantiated by roentgen examination. Chronologically, symptoms of diabetes mellitus preceded those of diabetes insipidus. Increased elaboration of the diabetogenic hormone from the cells of the anterior lobe was believed to be responsible for the symptoms of diabetes mellitus. Interruption of at least one nerve tract to the posterior lobe was believed to be responsible for the symptoms of diabetes insipidus.

The concentrations of serum sodium and chloride were increased at many observations. The diagnostic significance of these abnormalities is stressed.

All of the precise tests of renal function except those for sodium and chloride clearance resulted in values within the normal range. The decreased clearance of sodium and chloride and the unimpaired clearance of inulin and creatinine suggest that the inherent defect in diabetes insipidus is increased reabsorption of sodium chloride by the renal tubules. Injection of solution of posterior pituitary corrected this dysfunction temporarily. Further evidence of increased reabsorption was the positive balance for sodium and chloride during the five periods of controlled intake and output.

Symptoms of thirst were severe when the concentrations of serum sodium and chloride were increased simultaneously. Large changes in volume of plasma or interstitial fluid did not accompany aggravation or alleviation of this distressing symptom.

The patient described in this study was referred to us by Dr. James H. Townsend. Dr. Homer Smith helped with the preparation of the manuscript.

ARTERIAL BLOOD PRESSURE IN CASES OF AURICULAR FIBRILLATION, MEASURED DIRECTLY

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It is well recognized clinically that in patients having auricular fibrillation or flutter with grossly irregular pulses determinations of the blood pressure by the ordinary auscultatory and palpatory methods not only are difficult to obtain but are subject to considerable error. Several methods have been suggested by which the average systolic blood pressure may be obtained,[1] and these, in general, are based on the number of pulse beats which come through or fail to come through at different cuff pressures. These indirect methods require two observers and laborious calculations, and their significance may be questioned on theoretic grounds. Because of this unsatisfactory situation we felt it desirable to reinvestigate this subject by actually determining the blood pressure directly by intra-arterial puncture. This we felt would permit us not only to obtain the actual values but to establish the factors responsible for their variation from beat to beat.

The Hamilton needle manometer, recently developed,[2] was available for this purpose. It has been definitely shown to be an accurate instrument and has been used by Woodbury, Robinow and Hamilton [3] in studies on man.

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From the Cardiovascular Department, Michael Reese Hospital.

Read in preliminary form before the Central Society for Clinical Research, Chicago, Nov. 4, 1939.

1. Silberberg, M. D.: A Note on Blood Pressure Readings in Cases of Auricular Fibrillation, Brit. M. J. **1**:775, 1912. James, W. B., and Hart, T. S.: Auricular Fibrillation: Clinical Observations on Pulse Deficit, Digitalis and Blood Pressure, Am. J. M. Sc. **147**:63 (Jan.) 1914. Kilgore, E. S.: The Fractional Method of Blood Pressure Determination: A Contribution to the Study of Blood Pressure in Cardiac Arrhythmias, Arch. Int. Med. **16**:939 (Dec.) 1915.

2. Hamilton, W. F.; Brewer, G., and Brotman, I.: Pressure Pulse Contours in the Intact Animal: Analytical Description of a New High-Frequency Hypodermic Manometer with Illustrative Curves of Simultaneous Arterial and Intra-Cardiac Pressures, Am. J. Physiol. **107**:427 (Feb.) 1934.

3. Woodbury, R. A.; Robinow, M., and Hamilton, W. F.: Blood Pressure Studies on Infants, Am. J. Physiol. **122**:472 (May) 1938.

METHOD

The modification of the Hamilton manometer devised by Jochim and Gaddas[4] is shown in figure 1. The equipment is mounted rigidly on a heavy jack (*J*) with a three point contact (*X*), one part of which is adjustable with the floor. The Hamilton manometer is lined up with the electrocardiograph machine so that it will record on one half of the photosensitive paper in a manner similar to the arrangement devised for other purposes in this laboratory.[5] An ordinary 6 volt automobile headlight bulb is mounted in a housing (*A*) with a narrow vertical

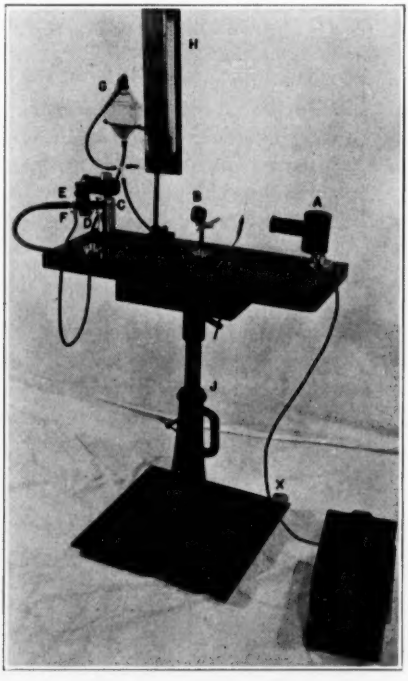

Fig. 1.—Photograph of the modification of the Hamilton manometer assembly, designed by Jochim and Gaddas and used in this study. See text for discussion.

slit in front. The image of the slit is converged by a double convex lens (*B*) and directed onto a planoconcave mirror (*C*) on the manometer, which reflects the image back onto the slit of the camera. By proper adjustment of the lens (*B*) the image of the slit can be sharply focused on the photosensitive paper. The manometer itself, which is an exact model of the one designed by Hamilton,

4. Jochim, K., and Gaddas, S. F.: Unpublished data.

5. Jochim, K.; Gaddas, S. F., and Marquis, H.: A Mobile Unit for Simultaneously Recording Heart Sounds, Pulse Tracing and Electrocardiogram, Am. Heart J. **13**:731 (June) 1937.

is held rigidly in a metal tube (*D*) and supported by eight adjustable screws which can shift its direction. The metal tube is mounted rigidly on an upright bar by means of a tight-fitting clamp (*E*) so that the level of the manometer mirror (*C*) can be brought into the same plane as the optical axis of the electrocardiographic machine, thereby avoiding parallax. Cruder vertical adjustment is possible with the heavy jack. The whole unit is mobile. Silver membranes of

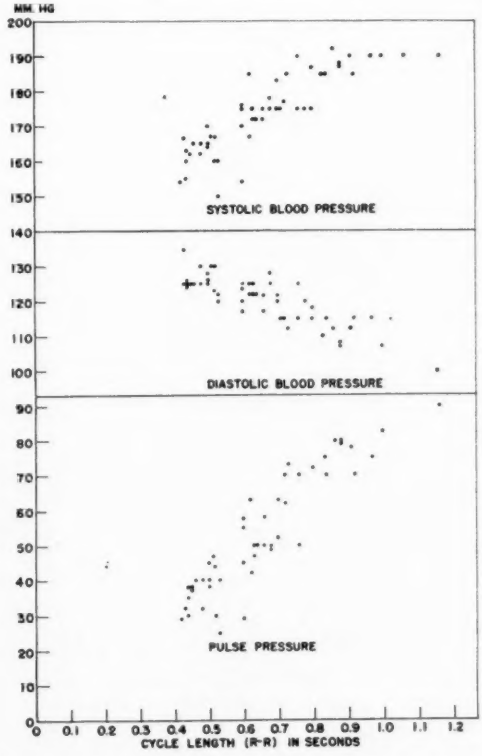

Fig. 2.—Chart showing the relation of systolic, diastolic and pulse pressure to cycle length in 50 successive beats of the heart of a patient with auricular fibrillation (a portion of whose record is shown in figure 6 *C*). Ordinates, millimeters of mercury; abscissas, seconds. See text for discussion.

appropriate sensitivity, prepared by Mr. S. Rodbard, were employed to prevent distortion of the pressure curves. By means of a stopcock (*F*) the manometer is connected to a citrate leveling reservoir (*G*) and a mercury manometer (*H*) for calibration.

The system is sterilized by filling it for several days before use with a solution of 70 per cent alcohol. The alcohol is then replaced by a sterile solution of 4 per cent sodium citrate from which the air has been previously boiled off. This is

layered with sterile liquid petrolatum to keep the system free of air and to prevent it from becoming underdamped.

The subject is permitted to lie comfortably in the recumbent or semiprone position, and the electrocardiographic leads are applied (leads II or III). A 20 gage needle soldered to an attachment which is screwed to the lead manometer tubing is inserted into the brachial artery after the skin has been previously sterilized with alcohol and anesthetized with a 1 per cent solution of procaine

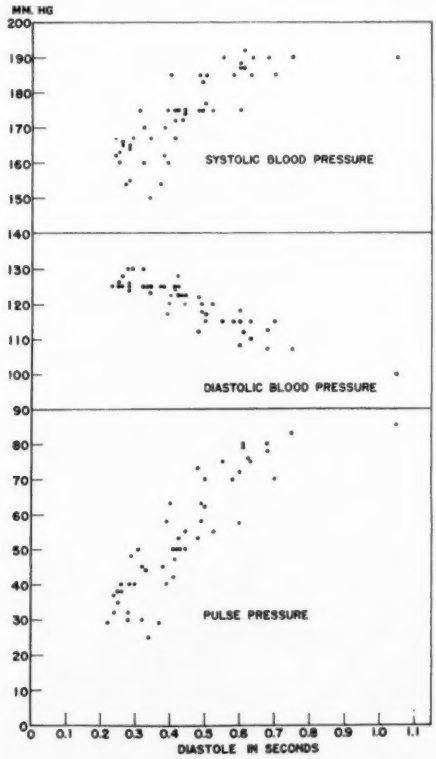

Fig. 3.—Chart constructed as in figure 2, relating the variables to the preceding diastole. See text for discussion.

hydrochloride. The appearance of pulsations of the image on the camera slit indicates that the needle is in the artery. After a record of the pressure has been taken simultaneously with the electrocardiogram, the pressure manometer is calibrated in the usual manner,[6] and the calibration is photographed so that the pressure levels can be quantitated.

6. Katz, L. N.; Friedman, M.; Rodbard, S., and Weinstein, W.: Observations on the Genesis of Renal Hypertension, Am. Heart J. **17**:334 (March) 1939.

The clinical material was obtained from the medical wards of the hospital and the adult cardiac clinic of the Mandel Clinic. Ten patients were used in this study. All were suffering from organic heart disease; in 6 it was of the rheumatic type, and in 4, of the arteriosclerotic type. Eight had chronic auricular fibrillation, 1 had chronic auricular flutter and 1 had sinus rhythm with a pulsus trigeminus due to regularly recurring auricular extrasystoles. (In addition, records were taken of several other patients with sinus rhythm [cf. fig. 14] and of others with frequent extrasystoles [cf. fig. 11].) Mitral stenosis was present in 3 of these patients and aortic insufficiency in 2. Two patients had marked hypertension. The ventricular rate in these patients at the time the records were obtained ranged

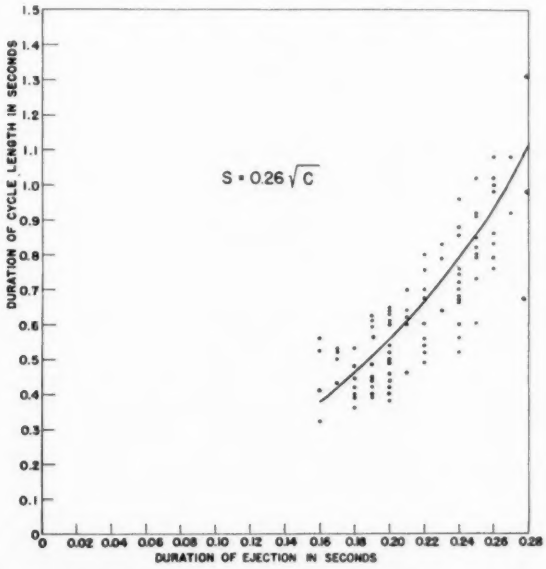

Fig. 4.—Chart relating the duration of ejection (abscissas) to the cycle length (ordinates) of 150 beats of the heart of a patient, portions of whose records are shown in figure 6 (*A*, *B* and *C*). The curve connects the means, and the equation for this curve is given in the chart. See text for discussion.

from an average rate of 161 beats per minute (cf. fig. 8 *A*) to 36 beats per minute (cf. fig. 8 *C*) in a case of auricular fibrillation with almost complete heart block due to digitalis excess. Two patients entered the hospital with severe congestive failure, and several records were taken on them during the course of clinical improvement (cf. fig. 6).

In each record the following measurements were made in 50 consecutive beats (cf. fig. 14 *A*): (1) the cycle length from the RR interval of the electrocardiogram, lead II or III, (2) the maximum systolic pressure from the peak (*b*) of the pressure pulse curve, (3) the minimum diastolic pressure from the lowest point, *a*, on the pressure pulse curve, (4) the duration of ejection from the beginning of the upstroke of the pressure pulse curve to the bottom of the incisura

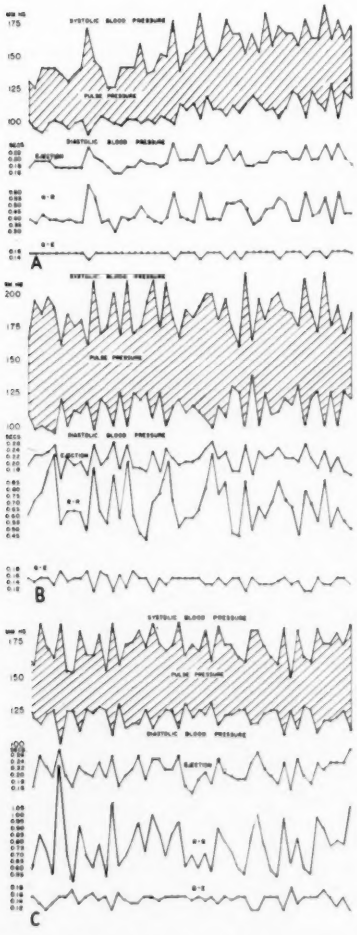

Fig. 5.—Charts showing the systolic blood pressure (uppermost curve), diastolic blood pressure (curve below), pulse pressure (shaded area), duration of ejection, RR interval and QE duration (successively lower curves) in 50 successive beats of the heart of a patient, portions of whose original record are shown in figure 6. Each beat is plotted in succession. The ordinates give millimeters of mercury for the pressures and seconds for the other measurements. The record in chart *A* was taken during heart failure; those in charts *B* and *C*, at two stages during recovery from heart failure. The method of determining these variables and their interpretation are discussed in the text.

(*a-c*), (5) the duration of diastole (and isometric contraction period) from the bottom of the incisura to the beginning of the upstroke of the pressure pulse (*c-a*) and (6) the QE interval, i.e., the interval between the beginning of QRS in the electrocardiogram to the upstroke of the pressure pulse curve (*Q-a*). The durations were determined in hundredths of a second and the pressures in millimeters of mercury.

The relation of the following factors to preceding cycle length and to the diastole preceding the measurement was analyzed: (*a*) systolic pressure, (*b*) diastolic pressure, (*c*) pulse pressure (computed by the difference between systolic and diastolic pressure), and (*d*) QE interval. These were assembled in tabular form, and graphs were then constructed to illustrate the relation. Other graphs

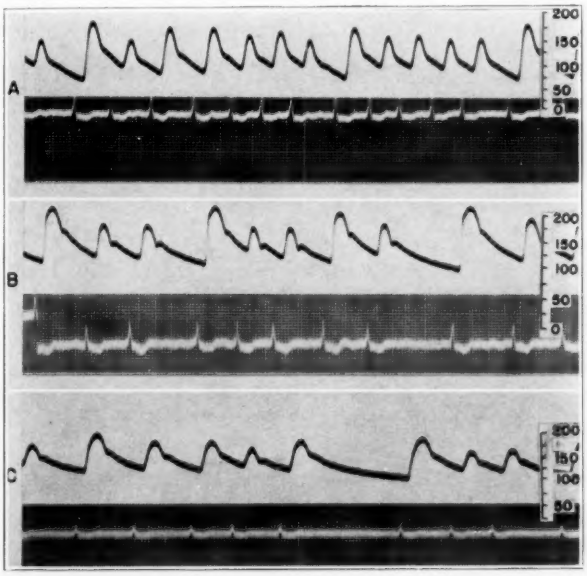

Fig. 6.—Portions of the original records (reduced) of a patient with auricular fibrillation at various stages of heart failure (*A*, maximum; *B*, intermediate; *C*, minimum). In each the direct pressure curve from the brachial artery is shown by the upper black curve; the calibration in millimeters of mercury is shown on the right. The standardized electrocardiogram, lead II, is shown by the white curve in each (time, 0.04 and 0.2 seconds). Each horizontal white line represents 0.1 millivolt.

were made to show the relation of the duration of ejection to the cycle length; when the variations in the latter were great enough a curve of the mean values was drawn, and the value for K which made the best fit to the curve was derived (by Mr. K. Jochim) by use of the formula $S = K \sqrt{C}$.[7]

7. Katz, L. N., and Feil, H. S.: Clinical Observations on the Dynamics of Ventricular Systole: Auricular Fibrillation, Arch. Int. Med. **32**:672 (Nov.) 1923.

RESULTS

An idea of the values for pressure is readily obtained by reference to our records (cf. figs. 6, 8 and 9). Superficial examination of the curves will show differences in both systolic and diastolic blood pressure with every beat during the irregular beating of the heart, the usual variation between successive beats being about 25 mm. of systolic pres-

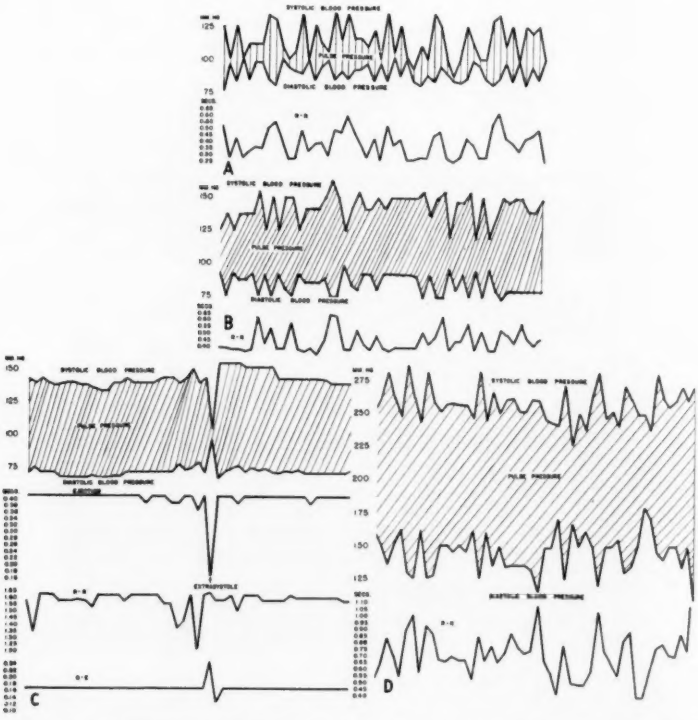

Fig. 7.—Charts constructed as in figure 5 and with the same conventions. Chart *B* is that of another patient, with auricular fibrillation and an average ventricular rate of 144 beats per minute. Chart *C* is that of a third patient, with auricular fibrillation and almost complete heart block, the average ventricular rate being 36 beats per minute. Chart *D* is that of a fourth patient, with auricular fibrillation and marked hypertension, the average ventricular rate being 90 beats per minute. In Chart *C* the time of occurence of an extrasystole is indicated. Portions of the original curves for these patients are shown in *B*, *C* and *D* of figure 8. See text for discussion.

sure and 15 mm. of diastolic pressure, but variations as great as 60 and 40 mm., respectively, being not infrequent. A definite relation is seen to exist between the cycle length and the levels of blood pressure, the

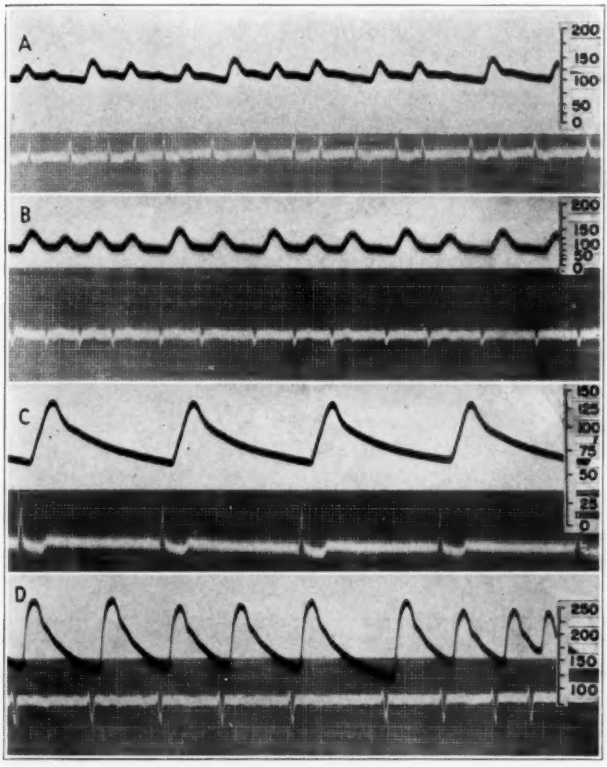

Fig. 8.—Portions of the original records (reduced) of 4 patients with auricular fibrillation. From the cases of the second, third and fourth of these the charts in figure 7 were constructed. The curves and conventions are as in figure 6, except that in *B* and *D* the electrocardiogram represents lead III.

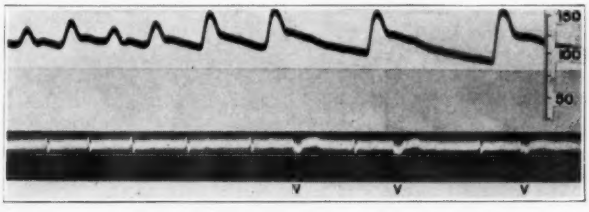

Fig. 9.—Portion of the original record (reduced) of a patient with auricular fibrillation and ventricular extrasystoles (*V*). The curves and conventions are as in figure 6. See text for discussion.

systolic blood pressure and pulse pressure bearing a direct relation to the preceding cycle, while the inverse holds for the diastolic pressure.

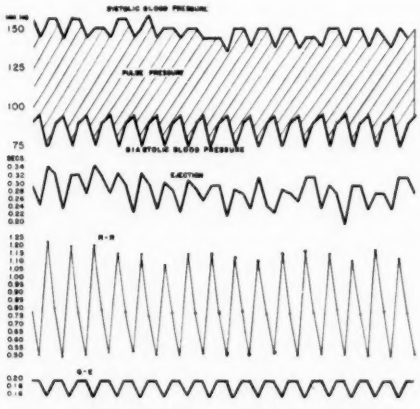

Fig. 10.—Chart constructed as in figure 5 and with the same conventions in the case of a patient with sinus rhythm and a persistent pulsus trigeminus due to a regularly recurring auricular extrasystole from the same focus; a portion of the original curve is shown in figure 11 *A*. See text for discussion.

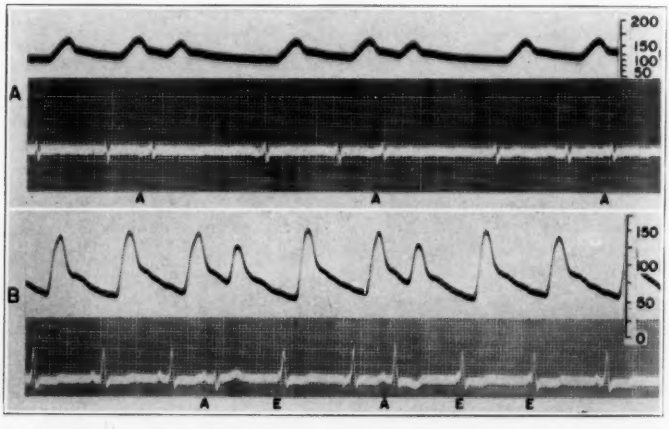

Fig. 11.—Portions of the original records (reduced) of 2 patients with sinus rhythm and auricular extrasystoles (*A*). The curves and conventions are as in figure 10. Record *A* is that of the patient on whom data are charted in figure 10. Record *B* is that of another patient with sinus rhythm and auricular extrasystoles showing aberrant conduction (*A*) and nodal escapes (*E*). See text for discussion.

This correlation can be seen more clearly from the graphs (figs. 2 and 3) in which these variables from 1 case, namely, systolic pressure, diastolic pressure and pulse pressure, are plotted for each of 50 successive beats against cycle length and against the duration of the diastole preceding the points used. Examination of these figures shows that the relation is not proportional, the relative amount of change being less marked with the longer cycles (diastoles) than with the shorter ones.

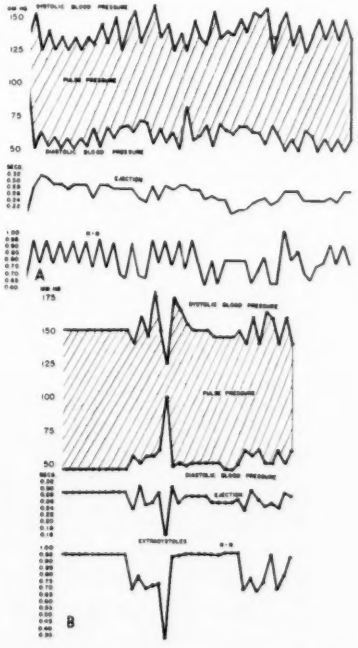

Fig. 12.—Charts constructed as in figure 5, with the same conventions, in the case of a patient with chronic auricular flutter. Portions of the original curves for this patient are shown in figure 13. The record in chart *A* was taken during a time when the auriculoventricular conduction was irregular, leading to irregular ventricular beating. That in chart *B* was taken during a period of regular auriculoventricular conduction interrupted by extrasystoles (as indicated) and followed by a final period of irregular ventricular beating. See text for discussion.

The duration of ejection, in all instances, was found to fit the square root formula ($S = K\sqrt{C}$) relating it to the cycle length. In the 4 cases in which the range of the cycle lengths was sufficiently great, K was found to be 0.23, 0.26, 0.26 and 0.26, respectively. In 1 of the latter,

150 beats were plotted (cf. fig. 4), obtained at three stages of heart failure, showing that the ventricular rate was the dominant factor in determining the duration of ejection.

In this last case, records taken at intervals as the patient recovered from heart failure and reestablished her preexisting hypertensive level gave us the opportunity to study all the aforementioned variables under these changing conditions. The correlations are clearly shown in figure 5 (*A*, *B* and *C*), which illustrates the pressures in successive beats and the duration of the intervals in the cardiac cycle from the records taken as she recovered from heart failure. It will be seen that her pulse pressure increased on the average as her heart failure lessened (cf. fig. 5, *A* and *B*), only to decrease again when her diastolic pressure had risen (cf. fig. 5, *B* and *C*). Obviously several factors operated in this patient to give this result: (1) the change in the contractile power of her heart, (2) the slowing of the heart rate and (3) the degree of distention of her arterial system. Slowing of the heart rate and improvement in the power of the heart might be expected to increase the pulse pressure. The decrease in pulse pressure in the third record must therefore be ascribed to the change in the diastolic blood pressure with its associated alteration in peripheral resistance and in resistance of the elastic reservoirs.[8] In figure 6 a few beats from each of the original records are reproduced for comparison. These curves illustrate the wide variation in pressure from beat to beat and, together with the other data we obtained, establish the large variation of pressure levels occurring in the irregular ventricular action of auricular fibrillation or flutter.

The effect of the ventricular rate on the blood pressure is illustrated in figure 7 (*B*, *C* and *D*). The diastolic pressure levels are approximately the same in all 3 cases; nevertheless, the systolic and pulse pressures show a remarkable variation. The difference in the average rate between *B* and *C* is only 27 beats per minute, and yet there is a striking reduction in systolic and pulse pressure at the faster rate. This is in contrast with the small difference in systolic and pulse pressure between *C* and *D*, despite the fact that the difference in rate is 108 per minute, or four times that between *B* and *C*. This tends to show that the variations in these pressure levels found in single patients apply also to the variations between different patients. Portions of the original curves are shown in figure 8.

The effect of regularity of action of the heart in removing the fluctuations in blood pressure is clearly shown in figure 7 *C*, in which, aside from the time when an extrasystole occurred, the pressures are seen to

8. Wiggers, C. J.: Dynamics of Hypertension, Am. Heart J. **16**:515 (Nov.) 1938.

be practically constant. The influence of the state of the elastic reservoirs (the aorta and the large arteries) on the pulse pressure is shown by comparing figure 7 *D* with figure 5 *C*.

That the influence of a short cycle length produced by extrasystoles is similar to that noted in auricular fibrillation is shown in figure 7 *C*, in which the premature beat with the reduced filling period preceding it is associated, as might be expected, with a rise in diastolic pressure and a fall in systolic and pulse pressure. However, the changes caused by the extrasystoles are too great to be explained only on this basis; they must be partly attributed to the less synergic contraction of the various elements in the left ventricle. This is shown further in figure 9, which illustrates a case in which extrasystoles (*V*) occurring no more pre-

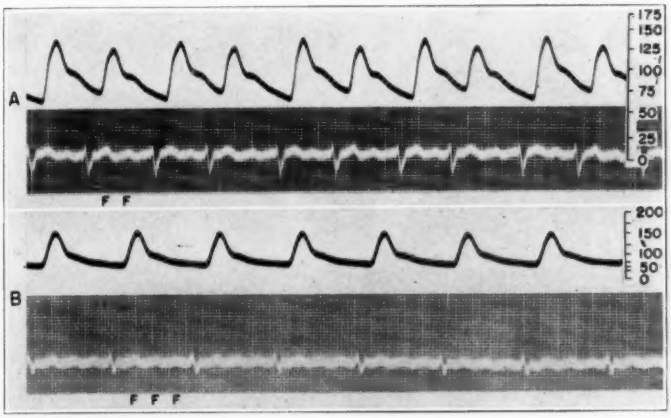

Fig. 13.—Portion of the original record (reduced) of the patient on whom data are charted in figure 12. The curves and conventions are as in figure 6, except that in *A* the electrocardiogram represents lead III. Record *A* represents a period of irregular ventricular beating; record *B*, a period of regular beating. *F* represents the auricular flutter waves.

maturely than some of the beats conducted through the auriculoventricular junctional tissue (second and third beats of the record) failed to open the semilunar valves and had no appreciable influence on the pulse curve. More careful analysis of our data has shown that influences similar to this but much less striking occur even among the conducted ventricular beats in auricular fibrillation (cf. fig. 8 *A*).

This influence of extrasystoles is clearly shown by the rhythmic variations in all the variables observed in a case in which persistent pulsus trigeminus (fig. 10) was present, the extrasystoles being auricular

in origin (cf. fig. 11 *A*). In figure 11 *B* is shown a portion of the record of another case, with auricular extrasystoles (*A*) having aberrant conduction and followed by nodal escapes (*E*).

The influence of regularity of the ventricular beating on these variables is clearly illustrated in the records obtained on the patient with auricular flutter. Figure 12 *A* shows the chart recorded during a period of continuously irregular ventricular beating in this patient; this resembles the changes noted in our cases with auricular fibrillation. Figure 12 *B* shows the constancy of values for blood pressure in a graphic repre-

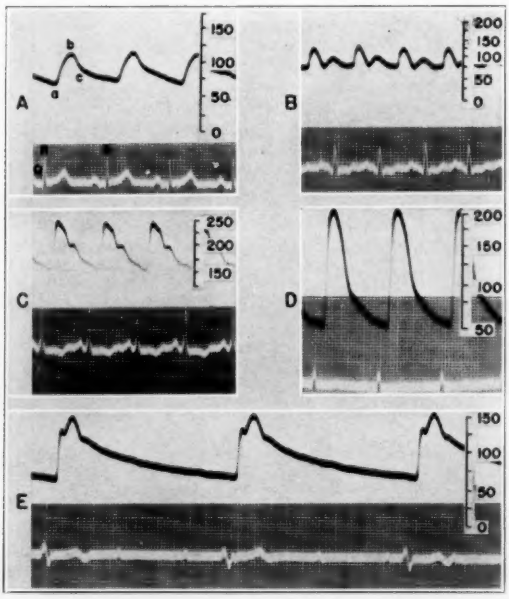

Fig. 14.—Portions of the original records (reduced) of 5 patients with sinus rhythm. Record *A* shows normal regular rhythm in a patient without cardiovascular disease. Record *B* shows sinus tachycardia in a patient with rheumatic heart disease. Record *C* shows sinus rhythm in a patient with essential hypertension. Record *D* shows sinus rhythm in a patient with a relatively free aortic valvular insufficiency of syphilitic origin. Record *E* shows a sinus rhythm and a slow idioventricular rhythm at a rate of 20 in a patient with complete auriculoventricular block on an arteriosclerotic basis. See text for discussion.

sentation of 50 successive beats in this case of flutter when the ventricular rate was regular. Fluctuations of blood pressure appeared only when this regularity was interrupted by extrasystoles (middle of curve) and by the development of irregular auriculoventricular conduction toward the

end of the record. Figure 13 illustrates portions of the original curves obtained in the case of this patient (*A*) with and (*B*) without irregular ventricular beating.

Figure 14 shows examples of the sort of records obtained with regular sinus rhythm: (*A*) of normal sinus rhythm in a patient without cardiovascular disease, (*B*) of sinus tachycardia in a patient with rheumatic heart disease, (*C*) of sinus rhythm in a patient with essential hypertension, (*D*) of sinus rhythm in a patient with a relatively free aortic valve insufficiency of syphilitic origin, and (*E*) of a sinus rhythm and a slow idioventricular rhythm at a rate of 20 in a patient with complete auriculoventricular block on an arteriosclerotic basis. These records again illustrate the constancy of blood pressure levels with regular beating of the ventricles, such as occurred in patients with auricular flutter and fibrillation when the ventricular rhythm was regular.

COMMENT

Systolic, Diastolic and Pulse Pressure.—The results on the variation in blood pressure are in close agreement with those obtained by Wiggers [9] in experiments on the dog. The differences in pulse pressure also agree with the variations in pulse amplitude reported by Katz and Feil [7] and lend support to the view that pulse amplitude is determined by pulse pressure.

Comparisons of either successive beats for individual patients or records for various patients indicate that the duration of the preceding cardiac cycle (and particularly the period of diastole, when the left ventricle can fill) is the most important factor governing the pressure levels. This relation with the systolic and pulse pressure is a direct one, and with the diastolic pressure, an inverse one. The effect of cycle length and filling time is not equal for equal increments at slow and rapid heart rates. A change in their duration when the heart rate is rapid has a much greater influence than a similar change when the heart rate is slower. This is in accord with the dynamics of filling of the ventricles as demonstrated by Wiggers and Katz [10] and would indicate that a similar pattern of filling actually occurs in man. Sufficient evidence has been presented to show that other influences appear to operate in cases of auricular fibrillation, as is shown by the wide scatter of systolic and pulse pressure at a given cycle length. Among these must be considered the manner of summation of the fractionate contractions [11]

9. Wiggers, C. J.: Studies on the Pathological Physiology of the Heart: The Intra-Auricular, Intraventricular, and Aortic Pressure Curves in Auricular Fibrillation, Arch. Int. Med. **15**:77 (Jan.) 1915.

10. Wiggers, C. J., and Katz, L. N.: The Contour of the Ventricular Volume Curves Under Different Conditions, Am. J. Physiol. **58**:439 (Jan.) 1922.

11. Wiggers, C. J.: The Muscular Reactions of the Mammalian Ventricles to Artificial Surface Stimuli, Am. J. Physiol. **73**:346 (July) 1925.

from beat to beat. Evidence for this last factor may be found also in the variation in contour and duration of the QRS complex in the presence of auricular fibrillation, especially at rapid rates. That such a factor could operate is supported by the results found with ventricular extrasystoles, with which an unexpected small pulse pressure and low systolic pressure—up to the points where the valves are not even opened—are found at cycle lengths at which other beats were more effective (cf. fig. 9). This has also been found to apply to experimental extrasystoles.[11]

The inverse relation of diastolic pressure to cycle length is to be expected, since the emptying of the elastic reservoirs into the small terminal arterioles and capillaries occurs during diastole. Variations in the relation might be expected on the basis that the central arteries are not filled to an equal extent at every systole. Such variations do occur, as can be seen by a casual inspection of the pressure curves. In short, the level of fulness of the central arteries as expressed by the pressure at the beginning of diastole is determined by what has happened during a number of preceding cycles.[9]

Obviously other factors, like respiration and reflex fluctuations in peripheral vasoconstriction, play an additional role in determining the levels of all of these pressures. For example, in figure 5 *A* a progressive rise in the general pressure levels, presumably due to peripheral vasoconstriction, was observed.

Our study has also shown that the properties of the elastic reservoirs (the aorta and the large central arteries) play a large role in cases of auricular fibrillation, as in cases of sinus rhythm,[8] in determining the systolic and pulse pressure values.

Pulse Wave Contour.—Not only the level of pressure but the pulse contour is altered by the cycle length. After all, the systolic and diastolic pressures represent only two points on the pressure curve and obviously do not give all the information obtainable from the entire curve. This is in accord with what has been observed in experimental animals,[9] and the causes are presumably the same. It is important to emphasize that the position of the maximum systolic pressure occurs at different times in systole and that its value relative to the end systolic pressure is variable. The shorter the cycle length, the greater is the tendency for the pulse to become smoother, to have its summit earlier and to have the closure of the semilunar valves at a lower level relative to the summit.

Duration of Ejection.—One of the variables which we have analyzed is the time occupied by ejection. In this we have confirmed the observa-

tions of Wiggers and Katz [12] and Katz [13] on experimental animals and of Katz and Feil [7] on man. Our results show that the formula $S = K\sqrt{C}$ (when S equals the period of ejection, C equals the cycle length and K is a constant) predicts reasonably the duration of the period of ejection, and the constant, which we found to be about 0.26, agrees fairly well with that obtained by these authors. The scatter from this predicted formula is not unexpected, considering that other factors also operate to determine the filling and emptying of the left ventricle. We have confirmed the established fact that the primary change which occurs with a changing heart rate and cycle length is in the diastolic period.

QE Interval.—The QE interval is determined by several factors.[14] On the one hand, it is altered by the duration of the isometric contraction period which occupies the first period of systole before ejection begins and which has been shown to vary directly with the level of the diastolic pressure preceding ejection [7]; it would be expected, therefore, to shorten the QE interval at the longer cycle length. On the other hand, the QE interval is also determined by the time it takes for the pulse to travel from the root of the aorta to the brachial artery, where the record of the pulse is taken. The evidence is clear [15] that the velocity of the pulse wave, which determines the time required to reach the brachial artery, is an inverse function of the diastolic pressure level; the lower the diastolic pressure, the slower is the pulse wave velocity. An examination of our data will show that the former factor is the dominant one, since a clear, though not consistent, tendency exists for the QE interval to be shortest when the diastolic pressure is lowest, namely, at the longest cycle length.

Implication of This Study.—This study has demonstrated that the blood pressure in cases of auricular fibrillation is variable in successive beats and that this variability is determined by the irregularity in the beating of the ventricle. It disappears when the beats become regular and is aggravated when extrasystoles are superimposed. The fluctuation of blood pressure becomes more pronounced the greater the arrhythmia of the ventricle. The faster the average ventricular rate, the greater the variability at a given degree of ventricular arrhythmia.

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12. Wiggers, C. J., and Katz, L. N.: Specific Influence of the Accelerator Nerves on Duration of Ventricular Systole, Am. J. Physiol. **53**:49 (Aug.) 1920.

13. Katz, L. N.: Factors Modifying the Duration of Ventricular Systole, J. Lab. & Clin. Med. **6**:291-311 (March) 1921.

14. Katz, L. N.; Landt, H., and Bohning, A.: The Delay in the Onset of Ejection of the Left Ventricle in Bundle Branch Block, Am. Heart J. **10**:681 (July) 1935.

15. Wiggers, C. J.: Physical and Physiological Aspects of Arteriosclerosis and Hypertension, Ann. Int. Med. **6**:12 (July) 1932. Bazett, H. C., and Dreyer, N. B.: Measurements of Pulse Wave Velocity, Am. J. Physiol. **63**:94 (Dec.) 1922.

Our observations incline us to the view that blood pressure in patients with auricular fibrillation having irregular beating of the heart cannot be determined by ordinary clinical means with any degree of accuracy. Our implication is not that the existence of hypertension or of the large pulse pressure in free aortic regurgitation cannot be ascertained in patients with this arrhythmia but that a more precise definition of the pressure values is subject to considerable error. The slower the ventricular rate and the less irregular its beating, the more precisely can these pressure values be defined. It is our belief from our study that the more laborious statistical methods of obtaining systolic blood pressure are probably no better than the ordinary means employed; at least, they do not justify the effort involved. For ordinary purposes the clinician must recognize the crudity of his determination, and when it is imperative to determine the pressure more precisely, which is rare, recourse may be had to a direct method, such as we have described.

SUMMARY

The blood pressure has been recorded in cases of auricular fibrillation in man by a direct method.

Fluctuations of blood pressure occur from beat to beat in cases of auricular fibrillation and other irregularities of the heart. The systolic and pulse pressure show a direct relation and the diastolic pressure an inverse relation to the preceding cycle length.

The QE interval was measured and found to shorten with the longer cycle lengths.

The duration of ejection fits the formula $S = K\sqrt{C}$, and in 4 of our cases in which a curve of means could be drawn K equaled 0.26, 0.26, 0.26 and 0.23.

In cases of auricular fibrillation and flutter with regular rhythm the values for blood pressure are nearly constant.

Extrasystoles are found to obey the same relation to the preceding cycle length as that found with auricular fibrillation and flutter, but in their presence additional factors play some role.

These results confirm and extend results obtained with the experimental animal and those in man based on accurate recording of the pulse. They indicate that pulse pressure determines pulse amplitude and that pulse contour is a mirror of the variations in internal pressure during the cardiac cycle at the site where the pulse is recorded.

Our results definitely show that it is impossible to obtain accurate determinations of blood pressure by any of the indirect methods when the pulse is grossly irregular.

Dr. Louis N. Katz furnished guidance in this study and advice in preparing the report. Mr. S. Rodbard gave technical assistance.

RENAL INVOLVEMENT IN DISSEMINATED LUPUS ERYTHEMATOSUS

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AND
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In recent years the disorder recognized as disseminated lupus erythematosus has become of increasing interest to internists and pathologists because of the widespread visceral and systemic involvement in the disease.

The dermatologic classification of lupus erythematosus and the diversified clinical manifestations of the disseminated form have been reviewed in several recent articles and will not be repeated at length here. It is sufficient briefly to summarize.[1] In contradistinction to the more common or discoid form of lupus erythematosus, the disseminated type, recognized as early as 1845 by Hebra and Cazenave, was established as a grave disease by Kaposi [2] in 1872. In 1895 Sir William Osler [3] stressed the importance of the systemic complications of a heterogeneous

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Abridgment of thesis submitted by Dr. Stickney to the faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Medicine

1. Engman, M. F.: Early Acute Lupus Erythematosus, Arch. Dermat. & Syph. **35**:685-697 (April) 1937. Goeckerman, W. H.: Lupus Erythematosus as a Systemic Disease, J. A. M. A. **80**:542-547 (Feb. 24) 1923. Hissard, M.: Le lupus érythémateux, Paris méd. **1**:373-378 (April 29) 1933. Keil, H.: Relationship Between Lupus Erythematosus and Tuberculosis: A Critical Review Based on Observations at Necropsy, Arch. Dermat. & Syph. **28**:765-779 (Dec.) 1933. Low, R. C., and Rutherford, A.: Post-Mortem Report of a Case of Lupus Erythematosus, Brit. J. Dermat. **32**:326-330 (Oct.) 1920. Lyon, J. M.: Acute Lupus Erythematosus, Am. J. Dis. Child. **45**:572-583 (March) 1933. Madden, J. F.: Acute Disseminated Lupus Erythematosus, Arch. Dermat. & Syph. **25**: 854-875 (May) 1932. O'Leary, P. A.: Disseminated Lupus Erythematosus, Minnesota Med. **17**:637-644 (Nov.) 1934. Pels, I. R.: Review of Lupus Erythematosus Disseminatus, Internat. Clin. **4**:273-298 (Dec.) 1933. Rose, E., and Pillsbury, D. M.: Acute Disseminated Lupus Erythematosus—Systemic Disease, Ann. Int. Med. **12**:951-963 (Jan.) 1939. Roxburgh, A. C.: Acute Disseminated Lupus Erythematosus: Five Fatal Cases, Brit. J. Dermat. **45**:95-109 (March) 1933. Stokes, J. H.: Case III: The Diagnosis of Disseminated Erythematosus Lupus, M. Clin. North America **10**:290-294 (Sept.) 1926.

2. Kaposi, M.: Neue Beiträge zur Kenntniss des Lupus erythematosus, Arch. f. Dermat. u. Syph. **4**:36-78, 1872.

3. Osler, W.: On the Visceral Complications of Erythema Exudativum Multiforme, Am. J. M. Sc. **110**:629-646 (Dec.) 1895.

series of conditions called the erythema group. Some, but probably not all, of these were disseminated lupus erythematosus. In 1922 Ehrmann and Falkenstein [4] were able to gather from the literature only 65 authentic cases in which there were necropsy records.

The disease occurs in the third and fourth decades, and the majority of patients are women. The role of tuberculosis as an etiologic factor has been fairly well disproved, but chronic infection of some type, frequently streptococcic, is important in the development of the disease. Exposure to light, mild injuries and irritants and allergy are considered to play an important part. The duration of the disease varies from a few weeks to several years. The prognosis is very poor. The initial signs may be cutaneous or systemic, and localized discoid lupus erythematosus may have been present for many years before dissemination takes place. Involvement of synovial and serous membranes and depression of bone marrow function with anemia, leukopenia, thrombopenia and abnormal leukocytes are common. There may be a generalized enlargement of the lymph nodes. Gastrointestinal symptoms and abdominal pain may necessitate a differentiation from a condition requiring surgical treatment. Endocarditis is frequently noted and has been extensively studied by Libman and Sacks,[5] who have described a nonbacterial verrucous endocarditis. Bronchopneumonia is the usual terminal event. Clinical evidence of visceral damage is most commonly found in the urine. Albuminuria is almost always present at some time during the course of the disease, and with this there is usually a moderate number of erythrocytes and casts in the urine. These observations always lead to a consideration of the question of the presence of acute or chronic glomerulonephritis. Edema may be present, but it is usually limited to the regions of cutaneous involvement. There is rarely any rise in blood pressure.

It is the purpose of this study to analyze the renal findings, both clinical and at necropsy, in 15 patients with disseminated lupus erythematosus who came to autopsy at the Mayo Clinic between Jan. 1, 1918 and July 1, 1939, inclusive. The diagnosis has been established in every instance histologically by biopsy or postmortem examination of the involved cutaneous regions according to the criteria of Goeckerman and Montgomery [6] and clinically according to the diagnosis formulated by the Section on Dermatology and Syphilology of the American Medical Association.

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4. Ehrmann, S., and Falkenstein, F.: Ueber Lupus erythematodes, Arch. f. Dermat. u. Syph. **141**:408-506 (Dec.) 1922.

5. Libman, E., and Sacks, B.: A Hitherto Undescribed Form of Valvular and Mural Endocarditis, Tr. A. Am. Physicians **38**:46-61, 1923.

6. Goeckerman, W. H., and Montgomery, H.: Lupus Erythematosus: An Evaluation of Histopathologic Examinations, Arch. Dermat. & Syph. **25**:304-316 (Feb.) 1932.

The data derived from study at the Mayo Clinic of these patients and others not dying at the clinic are contained in a review by Montgomery.[7]

The classification of these 15 patients, arranged according to O'Leary's criteria, is contained in table 1.

Three illustrative cases will be treated in some detail, and the entire 15 will be summarized in tables 2 and 3.

REPORT OF CASES

CASE 1.—A woman first registered at the clinic in 1926, at the age of 23, because of a scaling eruption on both cheeks and behind one ear. The lesions were described as sharply defined, maculopapular and scaling, with slight infiltration and epithelial plugging. A diagnosis of early discoid lupus erythematosus was made. The results of a general examination were negative. The blood pressure was 120 mm. of mercury systolic and 80 mm. diastolic; the concentra-

TABLE 1.—*Distribution According to Age of Fifteen Patients with Disseminated Lupus Erythematosus on Whom Necropsy was Performed*

Age, Years	Acute			Subacute	Generalized Discoid
	Total	Male	Female		
0- 9	0	0	0	0	0
10-19	1	1	0	0	0
20-29	5	1	4	0	0
30-39	4	1	3	0	1 (male)
40-49	1	1	0	0	0
50-59	0	0	0	1 (female)	1 (female)
60-69	1	0	1	0	0
70-79	0	0	0	0	0
Total	12	4	8	1	2

tion of hemoglobin (Dare) was 76 per cent, and the leukocytes numbered 8,100 in each cubic millimeter of blood. The results of urinalysis were negative. The skin cleared under quinine therapy.

The patient was next seen on Dec. 8, 1937, when she was 35 years old. She had been well until one year before, when the eruption on her face had returned. Late in the summer of 1937 she was sunburned. This exposure was followed by another flare-up of the eruption and by pain, swelling and stiffness in several joints.

The results of the general examination were essentially negative except for enlargement of the joints of the hands and dull red, raised areas with some scaling on the upper lip and over the hands and arms. The tonsils and one tooth were infected. The blood pressure was 115 systolic and 70 diastolic; the urine contained albumin, graded 2 on a basis of 1 to 4, and occasional erythrocytes; the blood urea was 30 mg. per hundred cubic centimeters, and the urea clearance was 47.9 cc. with a volume of 94 cc. of urine. The hemoglobin measured 12.7 Gm. The erythrocytes numbered 4,000,000 and the leukocytes 5,000 in each cubic millimeter of blood. The sedimentation rate was 31 mm. The serum sulfates were 4.2 mg. per hundred cubic centimeters. The diagnosis was as follows: subacute disseminated lupus erythematosus; chronic diffuse nephritis; chronic infectious arthritis. The patient was advised to have the teeth and tonsils cared for only after the cutaneous lesions had improved.

7. Montgomery, H.: Unpublished data.

She returned home; and after the condition of the skin had improved somewhat, the tonsils were removed, in February 1938. She did very poorly after the tonsillectomy. Her throat remained sore, and the arthritis and the eruption became worse. New lesions appeared on her cheeks, forehead and neck.

She returned to the clinic on March 12, 1938. There were edema of the lips and cheeks and a maculopapular eruption on the forehead and neck. The temperature was 101 F. and the blood pressure 98 systolic and 75 diastolic. On urinalysis the specific gravity was found to be 1.010; the albumin was graded 3; the erythrocytes were graded 1, and the hyaline casts were graded 1. The blood urea was 42 mg. and the serum sulfates 6.7 mg. per hundred cubic centimeters. The hemoglobin measured 9.7 Gm. The erythrocytes numbered 3,850,000, the leukocytes 4,400 and the platelets 112,000 in each cubic millimeter of blood. The diagnosis was acute disseminated lupus erythematosus. During the next seventeen days the patient went steadily downhill. The temperature remained elevated; the hemoglobin fell except immediately after a transfusion, and the leukocyte count fell steadily to 2,100 in each cubic millimeter of blood. The urinary albumin was graded 4, and hyaline casts and erythrocytes were present in most of the specimens of urine examined. The serum protein was 4.7 mg. per hundred cubic centimeters. The urea rose to 202 mg. per hundred cubic centimeters. Examination of the ocular fundi gave negative results except for a slight narrowing of the arterioles. Cultures of blood and urine were negative; 0.0014 mg. of lead was present in 1 cc. of urine. No evidence of tuberculosis could be found. Sulfanilamide up to 75 grains (4.9 Gm.) per day was given, but the patient died on March 29, 1938 in a state of uremic coma.

At necropsy the anatomic diagnosis was as follows: lupus erythematosus; bronchopneumonia; anemia graded 2; fatty degeneration of the liver; abscess of the left kidney.

The kidneys together weighed 322 Gm. The external appearance was not significant except for small cysts, up to 0.8 mm. in diameter. The cut surfaces were not abnormal. In the cortex of the left kidney there was an abscess measuring 4 by 5 mm. In sections stained for lipoids there were occasional lipoid droplets in the epithelial cells of the convoluted tubules. In those stained with hematoxylin and eosin there were focal accumulations of lymphocytes and polymorphonuclear leukocytes in the cortical region. In the glomerular tufts there was an increase in the number of cells, with fewer erythrocytes than normal. In sections stained by the method of Mallory as modified by Heidenhain (fig. 1) the cellular increase was seen to be endothelial, and many fibers of intracapillary connective tissue were present. The basement membrane was irregular and in many regions increased in thickness. There were no significant changes in the arterioles.

Case 2.—A woman, aged 22 years, was first admitted to the Mayo Clinic on June 1, 1929. Nine months before she had had an attack of diarrhea and vomiting, and a red eruption had appeared over the left cheek and about the eyelids. This spread to involve the other cheek and the bridge of the nose. Six months previously she had become jaundiced, with some pain in the right upper abdominal quadrant and light-colored stools. The jaundice cleared two weeks before admission, but the weakness and pallor became more marked. Shortly before admission, ultraviolet radiation was used on the skin, and this treatment was followed by a spread of the lesions to the neck, upper part of the chest, back, arms, elbows and fingers.

There was marked pallor with a slight icteric tinge. Over the whole precordium there was a systolic thrill with a loud systolic murmur over the apex, but the heart was not enlarged. Both the spleen and the liver were easily palpated.

The face was covered with ill defined erythematous plaques to which adhered a fine scale that left keratotic plugs on removal. Over the rest of the body there were discrete and confluent papules and macules of a pink color with fine white scales. The temperature was 102 F. The patient was admitted directly to the hospital.

The blood pressure was 97 mm. of mercury systolic and 40 diastolic. The urine had a specific gravity of 1.010; it contained no albumin or casts but occasional erythrocytes. The concentration of hemoglobin (Dare) was 20 per cent; the erythrocytes numbered 990,000 and the leukocytes 7,200 in each cubic millimeter of blood. The fragility of the erythrocytes was normal; the serum bilirubin was 3.5 mg. per hundred cubic centimeters, and a blood smear showed 27 per cent lymphocytes and 2.5 per cent promyelocytes. A culture of the blood was negative. Agglutinations for Brucella abortus were negative. During the first two weeks the erythrocytes fell to 640,000, the hemoglobin to 15 per cent and the leukocytes

Fig. 1 (case 1).—Heidenhain modification of Mallory stain (× 450). Acute disseminated lupus erythematosus. Foci of increase in thickness of the basement membrane with fibers of intracapillary connective tissue; proliferation of endothelial cells in glomerular capillaries. Acute glomerulonephritis (Bell).

to 6,200. Because of the immaturity of many of the white cells, leukemia with skin manifestations was suspected, but a biopsy of the skin established a diagnosis of acute lupus erythematosus.

During the next month the patient was given bone marrow, fetal liver and roentgen ray treatments. The hemoglobin rose to 30 per cent, with 1,590,000 erythrocytes, and there were 3,600 leukocytes, with 32 per cent lymphocytes. In the urinalysis the albumin was graded 1 to 2. No casts or erythrocytes were seen. The skin gradually cleared and the patient improved, but by August 13 she began to get worse. There followed two transfusions, after which she improved. By September 4 the hemoglobin was 40 per cent, and the erythrocytes numbered 2,290,000, the platelets 250,000 and the leukocytes 6,800, with very few immature

cells. For the first time, there was an increased fragility of the erythrocytes. The blood urea was 27 mg. per hundred cubic centimeters. The cutaneous lesions showed only residual pigmentation.

Soon after this there was a sudden turn for the worse. An abscess of a tooth was followed by a generalized enlargement of the lymph nodes. The leukocytes numbered 8,600 per cubic millimeter. A severe reaction with fever, diarrhea and jaundice followed a transfusion. The serum bilirubin rose to 14.6 mg., the urea to 52 mg. per hundred cubic centimeters and the leukocytes to 11,000 per cubic millimeter. The concentration of hemoglobin (Dare) fell to 15 per cent and the carbon dioxide–combining power to 15 per cent. The patient died on Oct. 3, 1929.

At necropsy the anatomic diagnosis was as follows: lupus erythematosus; splenomegaly (1,150 Gm.), with infarcts, anemia and icterus; hypertrophy of the liver (2,168 Gm.); terminal mitral vegetative endocarditis; fatty changes of the myocardium; iron pigmentation of the kidneys, lungs and lymph nodes.

The kidneys together weighed 301 Gm. There was nothing particularly abnormal in the gross appearance. In sections of the kidney stained for lipoids and with hematoxylin and eosin, as well as in those stained by the method of Mallory with Heidenhain's modification, there were occasional lipoid droplets in the epithelium of the convoluted tubules. Otherwise there were no significant changes. Sections stained for iron contained pigmented particles in the convoluted tubules.

CASE 3.—A girl, aged 16 years, was first seen at the Mayo Clinic in November 1916. An abscess of the neck had been incised in 1914, and in the months preceding admission there had been an itching, papular, generalized cutaneous eruption. The results of physical examination were negative except for the cutaneous lesions, for which a diagnosis of scabies was made. The results of urinalysis were negative except for an occasional leukocyte.

The patient was next seen on Sept. 8, 1920. She had been easily exhausted and short of breath for about two years, and in April 1920 had had an attack of abdominal pain, fever and diarrhea, which her physician had considered typhoid fever. With this there was some erythema of the face but no edema.

The patient was an undernourished person, with thinned hair. The ocular fundi were normal; the teeth and tonsils were infected. The blood pressure was 120 mm. of mercury systolic and 90 diastolic, and the temperature was 99 F. The concentration of hemoglobin (Dare) was 60 per cent; the erythrocytes numbered 3,550,000 and the leukocytes 7,600 in each cubic millimeter of blood. The Wassermann reaction was negative. The specific gravity of the urine was 1.026; the albumin was graded 4, and there were occasional hyaline casts and erythrocytes. The blood urea was 16 mg. per hundred cubic centimeters, and the return of phenolsulfonphthalein was 45 per cent. The diagnosis was chronic nephritis and acne rosacea.

On Sept. 20, 1920, tonsillectomy was performed. Recovery was uneventful for three days, but on the fourth day the temperature rose to 104 F. and the erythema of the face began to spread, to scale and to become edematous. On October 8 the diagnosis of disseminated lupus erythematosus was established. For the next four weeks the patient was under the care of the dermatologic and the nephritic service. The blood pressure averaged 120 systolic and 60 diastolic. The hemoglobin remained at 45 to 50 per cent; the erythrocytes varied from 2,700,000 to 3,700,000 and the leukocytes from 3,800 to 5,200 in each cubic millimeter of blood. The Widal reaction was negative. No tubercle bacilli were found in the urine, stools or sputum. Cultures of the blood were negative. A roentgenogram of the chest disclosed a lesion characteristic of tuberculosis in the upper lobe of the left lung.

Five teeth were infected apically. The urine during this period always contained albumin graded 2 or 3, occasional hyaline casts and about 10 leukocytes per microscopic field. The specific gravity of the urine varied from 1.001 to 1.024 in dilution and concentration tests. The excretion of phenolsulfonphthalein in two hours was 60, 70 and 80 per cent in three tests. The blood urea varied from 16 to 30 mg. and the creatinine from 1.2 to 1.3 mg. per hundred cubic centimeters. The results of an examination of the ocular fundi were negative. The cutaneous lesions gradually cleared, and on Nov. 6, 1920 the patient was sent home, on an antituberculosis regimen.

She returned two months later because of a recurrence of the cutaneous lesions. At times since her dismissal there had been edema of the face and legs. On Jan. 18, 1921 a radical alveolar resection of one molar was done. There was some exacerbation of the cutaneous lesions, but the temperature did not rise above 99 F. The blood urea was 34 mg. per hundred cubic centimeters; the leukocytes numbered 5,200 in each cubic millimeter of blood, and the urine contained albumin graded 3 and granular casts. Results of tests of kidney function were essentially the same as on the previous admission. She improved and was sent home again.

On July 6, 1921 the patient was admitted for the fourth and last time. She had been well until May, when she had become ill with an infection of the upper part of the respiratory tract. In June she had had a constant fever and edema of most of the body. The physician she had consulted at home reported "cotton wool" exudates in the retina and a precordial friction rub. On admission her temperature was 101 F., and there was a persistent erythema of the face with lesions on the hips and hands. Rales were heard over the base of each lung. The heart sounds were distant, without murmurs. The blood pressure was 116 systolic and 84 diastolic. There was no edema of the skin. The ocular fundi showed two areas of recent "cotton wool" exudate without edema or hemorrhage. On July 11 an impacted tooth was extracted without much reaction. During July there was not much change in temperature or blood pressure. The urine contained albumin, hyaline and granular casts and erythrocytes in all specimens. The excretion of phenolsulfonphthalein was 45 per cent, and the blood urea rose from 29 to 50 mg. per hundred cubic centimeters. The leukocytes rose from 5,200 to 9,400 in each cubic millimeter of blood. Cultures of the blood were negative, and the sputum contained no tubercle bacilli.

On August 6 an extensive bronchopneumonia developed; the patient rapidly became stuporous and died in convulsions on Aug. 11, 1921. The blood urea rose to 162 mg. per hundred cubic centimeters and the leukocytes to 11,600 in each cubic millimeter of blood the day before death.

At necropsy the anatomic diagnosis was as follows: disseminated lupus erythematosus; ulcerative tuberculous enteritis; caseating mesenteric lymph nodes containing tubercle bacilli; bilateral lobar pneumonia; bilateral fibrous pleuritis; miliary tuberculosis of the spleen.

The right kidney weighed 200 Gm. The external appearance was not significant, except that the markings were indistinct and the consistency was decreased. In sections of the kidney stained for lipoid none was found. In those stained with hematoxylin and eosin there were small focal accumulations of lymphocytes in the cortex. The epithelium of the convoluted and straight tubules was flattened, and the tubules, which also contained hyaline casts, were dilated. The glomerular capillaries contained fewer erythrocytes than normal, and there was an increased amount of eosin-staining hyaline material. In sections stained by the Heidenhain modification of the Mallory method the basement membrane was very irregular

and of about three times the normal thickness (fig. 2). The endothelial cells were decreased in number, and there were many fibers in intracapillary connective tissue.

The entire series of 15 cases is summarized in table 2.

THE RENAL LESIONS

In summary, the clinical evidence of renal damage in these 15 cases is interesting. In only 4 cases (1, 3, 4, 15) did the disease terminate in uremia, with a blood urea of more than 60 mg. per hundred cubic centimeters. In these and in 5 others (7, 9, 10, 11, 12) there were fairly constant albuminuria, microscopic hematuria and cylindruria. In most instances there was a considerable fluctuation in the urinary findings,

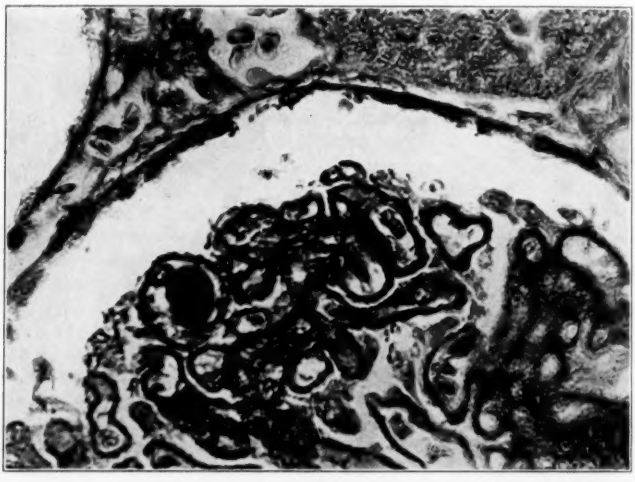

Fig. 2 (case 3).—Heidenhain modification of Mallory stain (× 525). Acute disseminated lupus erythematosus. Marked increase in thickness of the basement membrane; "wire loop" lesion as described by Baehr.

which quite closely paralleled the severity of the cutaneous symptoms. In 2 cases (2, 8) at no time was there more than slight albuminuria, and in 3 cases (5, 13, 14) there were no positive urinary findings. All studies of renal function which were carried out indicated good function until the final stages of the disease. In cases 4 and 15 albuminuria preceded the cutaneous lesions. In the other cases cutaneous symptoms preceded the albuminuria, and the time which elapsed between the known onset of albuminuria and death varied up to eighteen months.

In only 1 case (3) were there cotton wool exudates in the ocular fundi, and in 1 case (6) there were small hemorrhages. In 3 others (1, 4, 5) there was evidence of angiospasm in the retinal arterioles.

TABLE 2.—*Clinical Data in Fifteen Cases of Disseminated Lupus Erythematosus*

Case	Age	Sex	Duration Dissemination, Mo.	Maximum Blood Pressure	Leukocytes per Cu. Mm.		Blood Urea, Mg. per 100 Cc.	Urine—1-4			Summary
					Range	Average		Albumin	Red Blood Cells	Casts	
					Acute Disseminated Lupus Erythematosus						
1	35	F	17	115/ 70	2,100- 4,400	3,000	42 (202)*	4	2	2	Urea rose to 202 mg. per 100 cc. terminally; standard urea clearance 47.9 cc. 3 months before death; blood culture negative
2	22	F	12	97/ 40	3,500-11,000	6,500	27 (52)*	1-2	0	0	Many remissions; jaundice; exacerbation following ultraviolet light; anemia; marked lymphocytic immaturity
3	21	F	60	120/ 90	3,800- 9,400	6,200	16 (162)*	3	2	2	Many remissions; terminal rise in urea; urine negative during remissions; "cotton wool" exudates in fundi, P. S. P.† 45%, 60%, 70%, 80% on different occasions; active tuberculosis of lungs
4	34	F	48	170/120	3,000-21,000	7,300	34 (126)*	3	3	1	Many remissions; albuminuria preceded cutaneous symptoms; in fundus angiospasm of nephritic type; rise in urea only in last four days
5	24	F	1½	108/ 60	2,800- 4,200	3,600	.....	0	0	0	Joint symptoms, nine months; pleural and pericardial effusion; marked anemia
6	62	F	6	120/ 70	6,100- 8,800	6,900	28 (52)*	2	Occasional	0	Terminal hemiplegia; multiple emboli from thrombosis of iliac veins; in fundus hemorrhage without exudate
7	34	M	10	125/ 75	6,000-12,000	7,000	16 (50)*	2	Occasional	1	Multiple joint involvement; many petechiae; immature lymphocytes
8	21	F	9	120/ 76	2,200- 5,800	3,700	.....	1	Occasional	0	Remissions with negative urinary findings
9	31	F	9	154/ 82	4,100	4,100	16	1	2	0	Subacute bacterial endocarditis; blood culture, Streptococcus viridans
10	19	M	42	126/ 80	11,000-25,000	17,000	38	2	0	0	Exacerbation following roentgen treatment; many joint symptoms
11	27	M	3	130/ 50	2,700- 4,900	3,600	.....	2	0	0	Superimposed erythema multiforme; vegetative endocarditis
12	40	M	2 weeks	132/ 64	2,700-12,000	6,300	30	2	0	1	Lobar pneumonia; skin always sensitive to light; low grade fever and loss of weight for six months
					Subacute Disseminated Lupus Erythematosus						
13	58	F	15	130/ 74	9,100-19,000	14,000	.....	0	0	0	Died of pneumococcic meningitis
					Generalized Discoid Lupus Erythematosus						
14	33	M	60	105/ 60	3,400- 4,500	4,000	.....	0	0	0	Operated on for acute condition of gallbladder
15	55	F	16 years	178/140	4,500- 7,100	5,800	146	3	2	2	Albuminuria of twenty years' duration; chronic glomerulonephritis; cutaneous lesions inactive during terminal illness

* Terminal determination.
† Excretion of phenolsulfonphthalein.

Before the pathologic findings in the kidneys of this series are discussed it will be in point to review the pathologic reports in the literature.

Brooke in 1895 [8] described the appearance of the kidneys of a woman aged 33 years as follows: "The kidneys were enlarged with all the signs of soft white swelling. The kidney lesions were obviously merely acute supervening complications." Sequeira and Balean [9] in 1902 reported an autopsy as follows: "The microscope showed a condition of glomerulotubular nephritis of a fairly acute type with a slight increase in the connective tissue. The condition was not compatible with a nephritis of long standing such as would have been found had the affection dated back to the scarlet fever" (from which the patient had suffered six years before). Little [10] and MacLeod [11] called attention to "nephritis." Short [12] in 1907 reported a case in which the kidneys were very pale and mottled. There was "a chronic interstitial change in the epithelium with some glomerular tufts obliterated." There was also "hyaline thickening of the interlobular vessels." The 1 case in the series of Keith and Rowntree [13] in which necropsy was performed is included in this series as case 3. Keefer and Felty [14] in 1924 reported normal kidneys in 1 case (later revised by Jarcho [15]) and a chronic nephritis with fibrosis in another.

Baehr, Klemperer and Schifrin [16] reported 23 cases of disseminated lupus erythematosus in which necropsy was performed and found in 18 conspicuous glomerular changes, which they described as "proliferative

8. Brooke, H. G.: Lupus Erythematosus and Tuberculosis, Brit. J. Dermat. **7**:73-77 (Jan.) 1895.

9. Sequeira, J. H., and Balean, H.: Lupus Erythematosus: A Clinical Study of Seventy-One Cases, Brit. J. Dermat. **14**:367-387 (Oct.) 1902.

10. Little, G.: A Case of Lupus Erythematosus, Brit. J. Dermat. **17**:104 (March) 1905.

11. MacLeod, J. M. H.: Case of Lupus Erythematosus, Associated with Nephritis, Brit. J. Dermat. **20**:162-165 (May) 1908.

12. Short, T. S.: Fatal Cases of Acute Lupus Erythematosus, Brit. J. Dermat. **19**:271-274 (Aug.) 1907.

13. Keith, N. M., and Rowntree, L. G.: A Study of the Renal Complications of Disseminated Lupus Erythematosus: Report of Four Cases, Tr. A. Am. Physicians **37**:487-502, 1922.

14. Keefer, C. S., and Felty, A. R.: Acute Disseminated Lupus Erythematosus: Report of Three Fatal Cases, Bull. Johns Hopkins Hosp. **35**:294-304 (Sept.) 1924.

15. Jarcho, S.: Lupus Erythematosus Associated with Visceral Vascular Lesions: Series of Autopsied Cases, Bull. Johns Hopkins Hosp. **59**:262-273 (Oct.) 1936.

16. Baehr, G.; Klemperer, P., and Schifrin, A.: A Diffuse Disease of the Peripheral Circulation, Usually Associated with Lupus Erythematosus and Endocarditis, Tr. A. Am. Physicians **50**:139-155, 1935.

and thrombotic lesions of the glomerular loops, sometimes involving only segments and at times generalized, superficially resembling subacute bacterial endocarditis, but the rest of the affected glomerulus was not normal." Baehr and his associates described a hyaline thickening of the capillary wall called "a wire loop lesion." They regarded it as entirely different from the hyaline degeneration seen in chronic glomerulonephritis. Jarcho, and Denzer and Blumenthal [17] have confirmed these findings. In 1 of Jarcho's cases results of earlier examinations were reported as negative by Keefer and Felty.

Snapper [18] has written a chapter in "The Kidney in Health and Disease" on renal involvement in disseminated lupus erythematosus. He described swelling of the glomeruli with proliferation and swelling of the loops and cloudy swelling of the glomerular capsule, as well as interstitial abscesses. Mook and his associates [19] found 1 case in which the kidneys were of the primary contracted type, characteristic of hypertensive disease. Rose and Goldberg [20] reported a case with associated chronic arteriolar nephrosclerosis and another with "parenchymatous degeneration of the kidneys."

The pathologic findings in the present series are summarized in table 3. Histologic pictures of the kidneys in 4 cases are shown in figures 1, 2 and 3.

It will be noted that the weights of all the kidneys were normal or greater than normal, with a mean of 380 Gm. (organs with congenital cystic disease excluded). There are 3 cases in which there was definite hypertrophy (4, 7, 9), and in none of these was there much interstitial edema. In 2 of the 15 cases there was also hypertrophy of the liver. The absence of any contraction of the kidneys is consistent with the fact that severe hypertension was not found in this series. Likewise, the absence of significant changes in the renal arteries and arterioles is consistent with the clinical observations. The degree of generalized arteriosclerosis, except in patients of middle age, was not graded more than 1 on a basis of 1 to 4. Small miliary abscesses, such as were found in cases 1, 3 and 4, frequently occur in toxic diseases. A typical pyelonephritis was not found.

17. Denzer, B. S., and Blumenthal, S.: Acute Lupus Erythematosus Disseminatus, Am. J. Dis. Child. **53**:525-540 (Feb.) 1937.

18. Snapper, I.: Kidney Trouble in Acute Lupus Erythematosus, in Berglund, H., and Medes, G.: The Kidney in Health and Disease, in Contributions by Eminent Authorities, Philadelphia, Lea & Febiger, 1935, pp. 433-439.

19. Mook, W. H.; Weiss, R. S., and Bromberg, L. K.: Lupus Erythematosus Disseminatus, Arch. Dermat. & Syph. **24**:786-829 (Nov.) 1931.

20. Rose, E., and Goldberg, L. C.: The Visceral Lesions of Acute Disseminated Lupus Erythematosus, M. Clin. North America **19**:333-346 (July) 1935.

The most common significant histologic observation was an increase in the number of endothelial cells of the glomerular tufts with a reduc-

TABLE 3.—*Renal Changes Seen at Necropsy*

Case	Principal Cause of Death	Total Kidney Weight, Gm.	Glomeruli	Epithelium of the Tubules	Comment
			Acute disseminated lupus erythematosus		
1	Bronchopneumonia	322	Marked increase in endothelial cells; focal increase in thickness of basement membrane	Occasional lipoid droplets and hyaline casts	Focal interstitial lymphocytes and polymorphonuclear cells (fig. 1)
2	Bronchopneumonia; anemia	301	Essentially normal	Occasional lipoid droplets	Terminal vegetative endocarditis; hypertrophy of liver, spleen
3	Miliary tuberculosis	200 (1 kidney)	Irregular thickened basement membrane; hyaline masses in capillaries	Slight atrophy of convoluted tubules	Moderate number of interstitial lymphocytes; "wire loop" capillaries of kidney (fig. 2)
4	Bronchopneumonia; renal failure	485	Epithelial crescents in about 3%; occasional hyalinization	Focal regions of lipoids, hyaline casts; no marked atrophy	Hypertrophy of liver and heart; not typical chronic glomerulonephritis; multiple abscesses in both kidneys
5	Bronchopneumonia; anemia	292	Hyaline thrombi in capillaries; slight increase in thickness of basement membrane (fig. 3*A*)	Granular casts	Amyloid not present
6	Infarct of brain	322	Essentially normal except infarction	Essentially normal	Multiple emboli and infarcts
7	Bronchopneumonia	710	Slight increase in endothelial cells	Hyaline casts	Changes nowhere marked
8	Bronchopneumonia; anemia	277	Hyaline granules in capillaries	Granular casts	Fatty changes in myocardium and liver
9	Rheumatic endocarditis	465	Essentially normal (fig. 3 *B*)	Hyaline and granular casts	Lesions characteristic of bacterial endocarditis not found in kidneys
10	Bronchopneumonia	1,000	Essentially normal except for cysts	Lipoid droplets in cystic regions	Bilateral congenital cysts of kidneys
11	Vegetative endocarditis	390	Slight increase in endothelial cells	Essentially normal	Low grade pyelonephritis
12	Lobar pneumonia	378	Slight increase in endothelial cells	Essentially normal	No marked changes
			Subacute Disseminated Lupus Erythematosus		
13	Pneumococcic meningitis	260	Essentially normal	Occasional lipoid	Arterial changes consistent with age 58
			Generalized Discoid Lupus Erythematosus		
14	Miliary tuberculosis	Increased	Increase in endothelial cells	Essentially normal	"Large white kidneys"
15	Chronic glomerulonephritis	344	Hyalinization with many crescents	Atrophy with dilatation	Typical chronic glomerulonephritis

* Two kidneys present; only one kidney weighed.

tion of the number of erythrocytes in the capillary loops. Some degree of proliferation of endothelial cells was present in 6 cases (1, 4, 7, 11, 12, 14). The presence of hyaline eosin-staining material in the glomerular capillaries, noted in 5 cases (1, 3, 4, 5, 8), probably represents a

degenerative process. In 5 cases (1, 3, 4, 5, 12) there were definite fibers, which stained like and apparently derived from the basement membrane, seen within the glomerular capillaries in sections stained with

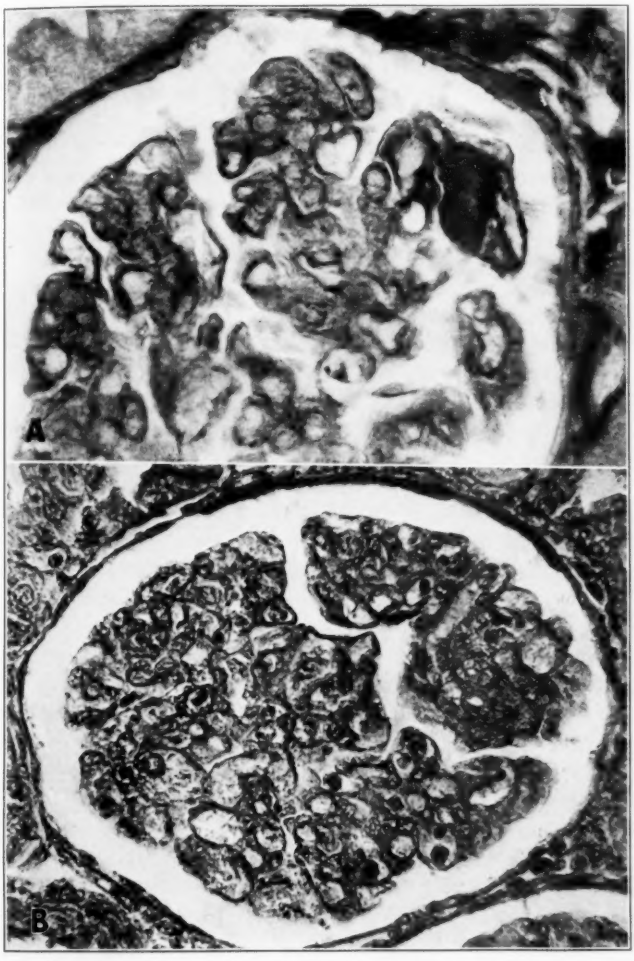

Fig. 3.—*A* (case 5), Heidenhain modification of Mallory stain (× 700). Acute disseminated lupus erythematosus. Hyaline masses in the glomerular capillaries entirely surrounded by basement membrane. *B* (case 9), Heidenhain modification of Mallory stain (× 450). Acute disseminated lupus erythematosus. Essentially normal glomerulus; clinically as severe a cutaneous and systemic disease as any of the others.

the azocarmine stain. Bell [21] has described such fibers in acute nephritis, and they will be discussed later. Tubular damage, except in regions related to infarction, was minimal throughout, although a few hyaline and granular casts were found in several cases. No significant deposit of lipoid was found, and there was no evidence of amyloidosis.

The inclusion of cases 14 and 15 in this series may be questioned. Both were instances of generalized discoid lupus erythematosus. In case 14 the renal findings were insignificant, but in case 15 there was chronic glomerulonephritis. The terminal events in the latter case were those of passive congestion and cardiac rather than renal failure. It is uncertain how long the renal disease had existed, but in 1914, fifteen years before death, a note had been made that there had been "kidney disease for nine years." A lesion on the scalp had been present since 1908. Although the albuminuria was constant, hypertension was not known to exist before the final admission. The cutaneous lesions were inactive during the terminal stages.

In order to compare the changes just summarized with those in other types of disease, a group of patients whose ages fell within the range of those in this series was collected; included were most of the patients between 20 and 45 years of age from whom kidney tissue was available. Eighty-five patients dying of various causes and coming to necropsy between Nov. 1, 1937 and Oct. 1, 1938 inclusive were selected. By study of sections of the kidney 11 of these were found to have renal changes comparable to those in most of the patients in the lupus erythematosus series. These changes are given in table 4, and these patients are referred to as the "control series."

The changes seen in most of the cases of disseminated lupus erythematosus are not similar to those seen in severe diseases of the kidney. The kidneys in the control series, which did not include any with known renal disease, showed changes as marked as most of those seen in the lupus erythematosus series (fig. 4), but the intracapillary hyaline changes were not seen in the control group.

Bell,[21] Dunn and McNee [22] and Keith and Thomson [23] have described changes in acute nephritis similar to those seen in disseminated lupus erythematosus. We refer to avascularity of the glomerulus, proliferation of the endothelial cells and irregularity of the basement membrane and presence of fibers within it. In all their cases the disease was of

21. Bell, E. T.: The Pathology and Pathogenesis of Clinical Acute Nephritis, Am. J. Path. **13**:497-552 (July) 1937.

22. Dunn, J. S., and McNee, J. W.: A Contribution to the Study of War Nephritis, Brit. M. J. **2**:745-751 (Dec. 8) 1917.

23. Keith, N. M., and Thomson, W. W. D.: War Nephritis: A Clinical, Functional and Pathological Study, J. Urol. **3**:87-139 (June) 1919.

short duration (a few days to three or four weeks), while in our cases of disseminated lupus erythematosus the average duration of the disease was sixteen and a half months and of the albuminuria six months.

The peculiar intracapillary hyaline thrombosis seen in our cases is similar to the lesion seen frequently in bacterial endocarditis and described by Löhlein,[24] Baehr [25] and Bell.[26] Its nature has led to much

TABLE 4.—*"Control Series" of Eighty-Five Patients Between Ages Twenty and Forty-Five*

Sex	Age	Cause of Death	Duration	Blood Urea, Mg. in 100 Cc.	Urine, Grade			Kidney Weight Gm.	Microscopic Changes in Kidneys
					Albumin	Casts	Erythrocytes		
M	25	Chronic ulcerative colitis with peritonitis	2 months	14	2	0	1	323	Increased endothelial cells with intracapillary fibers (fig. 4)
F	39	Staphylococcic septicemia	7 days	166	1	0	0	493	Irregular basement membrane; increase in endothelial cells
F	39	Fibroid uterus with peritonitis	2 weeks	32	2	2	3	267	Increase in endothelial cells
F	32	Brain tumor	10 days	26	0	0	0	234	Increase in endothelial cells
M	27	Chronic encephalitis	10 days	34	0	0	0	242	Increase in endothelial cells
M	33	Lobar pneumonia	10 days	*	2	2	2	241	Intracapillary fibers; increase in endothelial cells
F	42	Gangrene of colon	*	60	2	1	1	265	Increase in endothelial cells
F	35	Mitral endocarditis; cardiac decompensation	2 months	24	4	0	0	337	Increase in endothelial cells; infarction
M	22	Peritonitis	2 months	20	3	1	1	290	Increase in endothelial cells; intracapillary fibers
M	22	Chronic empyema	*	*	2	0	0	413	Increase in endothelial cells
F	38	Cirrhosis of liver	1 year	28	3	0	0	415	Increase in endothelial cells

* Unknown.

discussion. Bell expressed the belief that it comes from the lodgment of bacteria, but neither clinically nor pathologically has this theory been proved. In none of the present cases in which this lesion existed was an

24. Löhlein, M.: Ueber hämorrhagische Nierenaffektionen bei chronischer ulzeröser Endokarditis (Embolische neichteiterige Herdnephritis), Med. Klin. **1**: 375-379 (March 6) 1910.

25. Baehr, G.: The Significance of the Embolic Glomerular Lesions of Subacute Streptococcus Endocarditis, Arch. Int. Med. **27**:262-264 (Feb.) 1921.

26. Bell, E. T.: Glomerular Lesions Associated with Endocarditis, Am. J. Path. **8**:639-664 (Nov.) 1932.

organism cultured except by Welsh,[27] as mentioned in the case reports. Löhlein and Baehr expressed the opinion that the presence of bacteria can be demonstrated often enough to prove the hypothesis of bacterial origin in cases of bacterial endocarditis, but Baehr did not consider the lesion of disseminated lupus erythematosus to be similar to that of bacterial endocarditis. In the former disease all parts of the glomerulus are involved, while in the latter only a portion of the glomerulus is affected, according to Baehr.

If in disseminated lupus erythematosus the renal disorder we are dealing with is an acute glomerulonephritis, it must be concluded that the process is not of a duration coinciding with that of the albuminuria

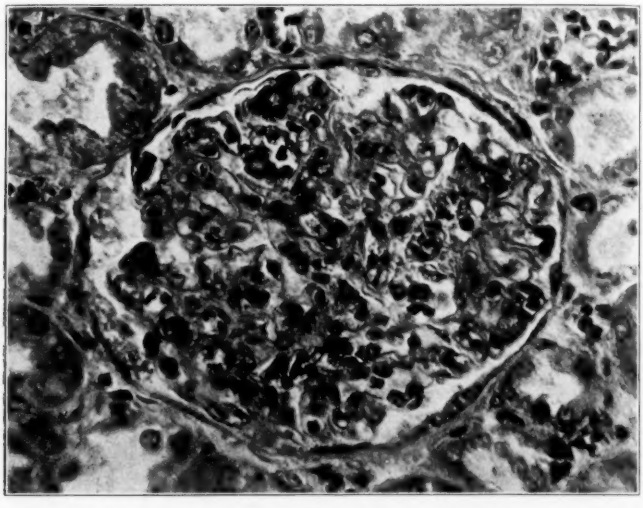

Fig. 4 (case 1).—Control series. Heidenhain modification of Mallory stain (×450). Death from chronic ulcerative colitis with generalized peritonitis; changes similar to those in figure 1; proliferation of the endothelial cells of the glomerular capillaries with intracapillary fibers.

and hematuria but that it is a terminal process. The other possibilities which might be considered are that the disorder is a peculiar variety of nephritis with a low grade of virulence or that it is a degenerative process secondary to a toxic debilitating disease. Mallory, in the discussion of Cabot[28] case 24201, expressed the opinion that the renal

27. Welsh, A. L.: Specificity of a Streptococcus Isolated from Patients with Pemphigus: Preliminary Report, Arch. Dermat. & Syph. **30**:611-630 (Nov.) 1934.

28. Acute Disseminated Lypus Erythematosus, Cabot Case 24201, New England J. Med. **218**:838-843 (May 19) 1938.

changes are not primary. The albuminuria of lupus erythematosus is not as constant or as severe as that seen in acute and chronic glomerulonephritis.

The relationship of the pathologic characteristics of the kidneys as described in preceding paragraphs to those of the cutaneous lesions in disseminated lupus erythematosus raises several interesting questions. Goeckerman and Montgomery have summarized what is commonly accepted as the histologic picture of the lesions. They emphasized dilatation of the capillaries and lymphatics, perivascular polymorphonuclear and lymphocytic infiltration, hyperkeratosis and edema of the cutis. They referred to the absence of proliferative vascular changes, but this Montgomery [29] has described as a change great enough to cause an obliteration of the smaller vessels. There is some thickening of the arterioles due to a mild proliferation of the endothelium and to edema, but there is no obliteration or organization. Hyaline changes are not seen.

In the kidneys the accumulations of lymphocytes, when present, are focal rather than perivascular. The endothelial proliferation is likewise never enough to cause obliteration of the vessels.

It may be of interest to mention a few of the observations made on hearts in this series of cases. Endocarditis in disseminated lupus erythematosus has been reported as a frequent occurrence by Weidman and Gilman.[30] Libman and Sacks described an atypical verrucous endocarditis, characterized by a fibrinous pericarditis and a valvular and mural endocarditis with small vegetations at the line of closure of any of the valves. No Aschoff bodies could be found. Baehr and his associates found that in 13 of their 23 cases there was associated nonrheumatic verrucous endocarditis, which in 5 instances extended to the mural endocardium. In our series there were 3 patients with endocarditis. From the blood of 1 patient Streptococcus viridans was cultured. From the other 2 patients evidence of bacterial origin of the endocarditis was not obtained, but the vegetations did not extend onto the mural endocardium.

SUMMARY

The visceral involvement in disseminated lupus erythematosus has been reviewed clinically. The pathologic changes in the kidneys in 15 fatal cases have been studied.

In 8 of the 15 cases there was no definite renal change except that seen terminally in debilitating disease.

29. Montgomery, H.: Personal communication to the authors.

30. Weidman, F. D., and Gilman, R. L.: A Case of Acute Disseminated Lupus Erythematosus: Necropsy Disclosing Acute Endocarditis, but not Tuberculosis, Brit. J. Dermat. **43**:641-647 (Dec.) 1931.

Without exception, the weight of the kidneys was normal or greater than normal. No contracted kidneys were found.

The most definite lesion was a proliferation of the endothelial cells of the glomerular capillaries. Hyaline thickening of these capillary walls and an irregularity and thickening of the basement membrane were also frequently present. These changes are somewhat similar to those which have been described in acute glomerulonephritis and the toxemias of pregnancy.

In 1 case in this series (case 15) there were pathologic changes characteristic of glomerulonephritis. The relationship of the changes noted to the lupus erythematosus is uncertain, since the renal disease preceded the cutaneous and the cutaneous lesions were inactive during the final illness.

In 1 other instance (case 4) there was some evidence of a subacute or early chronic glomerulonephritis. In this patient, too, the evidence of renal damage was known to have antedated the onset of the cutaneous lesions.

The arteries and arterioles were normal in most of the cases. In several there was slight thickening of the intima, but no thromboses were seen.

The changes in the tubules were of a minor nature.

CONCLUSIONS

A common distinct renal lesion does not exist.

Clinically, the duration of renal abnormality is much longer than the pathologic change would indicate; therefore, the disease either is not an ordinary glomerulonephritis or is of low virulence with slow progression. Probably the changes are secondary to toxic processes and do not represent primary renal disease. Similar changes were noted in the control group. The coincidence of cutaneous and renal exacerbations might lead to the conclusion that the pathologic findings were merely those of the recent terminal stage and that the previous renal flare-ups had subsided without scar. Even if this is true, the clinical history of the final stage is still longer than that of the usual acute glomerulonephritis.

MEASUREMENT OF VITAMIN A STATUS OF YOUNG ADULTS BY THE DARK ADAPTATION TECHNIC

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AND
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With the recognition that cases of mild, subclinical vitamin deficiency are much more common than cases of severe deficiency, the need for adequate diagnostic methods for early avitaminotic states is urgently felt by clinicians. Only by such methods can the clinician determine the borderline states of malnutrition that not only contribute to his patients' ill health but prevent the best response to therapeutic measures.

As a criterion of deficiency of vitamin A, the night blindness or dark adaptation test is valuable, especially since the work of Wald,[1] Wald and Clark,[2] Hecht and his co-workers [3] and others has demonstrated the physiologic role of vitamin A in the generation of the visual purple. Impairment of the visual cycle occurs as one of the first signs of an inadequate supply of vitamin A.

Jeghers [4] has reviewed the literature on this test, and Hecht [5] has reviewed the literature on rods, cones and the chemical basis of vision. Studies by various workers with different instruments include those of Jeans and Zentmire,[6] Jeans, Blanchard and Zentmire,[7] Edmund and Clemmesen [8] and Hecht and Mandelbaum.[9]

This research was supported by a grant from Anabolic Foods, Inc.

From the Department of Biological Sciences, Loyola University of Los Angeles.

1. Wald, G.: Carotenoids and the Visual Cycle, J. Gen. Physiol. **19**:351, 1935.

2. Wald, G., and Clark, A.: Visual Adaptation and Chemistry of the Rods, J. Gen. Physiol. **21**:93, 1937.

3. Hecht, S.; Chase, A. M.; Shlaer, S., and Haig, C.: The Regeneration of Visual Purple in Solution, Science **84**:331, 1936.

4. Jeghers, H.: Night Blindness as a Criterion of Vitamin A Deficiency: Review of Literature with Preliminary Observations of Degree and Prevalence of Vitamin A Deficiency Among Adults in Both Health and Disease, Ann. Int. Med. **10**:1304, 1937.

5. Hecht, S.: Rods, Cones and the Chemical Basis of Vision, Physiol. Rev. **17**:239, 1937.

6. Jeans, P. C., and Zentmire, Z.: A Clinical Method for Determining Moderate Degrees of Vitamin A Deficiency, J. A. M. A. **102**:892 (March 24) 1934.

(Footnotes continued on next page)

However, the reliability of earlier tests of dark adaptation has been questioned by many workers, and clinical results with various instruments have not shown sufficient correlation to warrant universal acceptance of the method. This is due mainly to the fact that certain instruments are not properly designed for positive detection of vitamin A deficiency. Others, though well suited to the purpose, are difficult to operate without some technical training. In the hands of inexperienced workers widely varying and hence inaccurate results are obtained. The sensitivity of different instruments also varies markedly, so that early deficiency states are not always perceived, and the patients are frequently classified as normal.

McCollum and his associates [10] concluded: "At present there seems to be widespread skepticism as to the reliability of the dark adaptation technic as a measure of vitamin A deficiency." There is little doubt, however, that the difficulty lies in the technic of the earlier tests; the fundamental principle seems well established that both the speed and the ultimate extent of dark adaptation bear a direct relation to the vitamin A supply of the body.

The regenometer was designed as a diagnostic instrument that would be sensitive and accurate in the detection of subclinical vitamin A deficiency and at the same time be simple to operate and require a minimum of time per test. Its action is first to break down the visual purple of the retinal rods by a bright light and then to measure the speed with which this rod pigment is regenerated. In this the regenometer differs somewhat from most other instruments used in detecting night blindness. It measures the length of time required for the subject to perceive light of a fixed intensity rather than the intensity that can be perceived at a given moment.

Our experimental object in studies with the regenometer was twofold: (1) to prove that by its use a subclinical vitamin A deficiency could be at least qualitatively detected, and (2) to determine its sensitivity in following the course of experimentally induced deficiency of vitamin A in normal subjects and the effect of vitamin A supplementation on this deficiency.

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7. Jeans, P. C.; Blanchard, E., and Zentmire, Z.: Dark Adaptation and Vitamin A: A New Photometric Technic, J. A. M. A. **108**:451 (Feb. 6) 1937.

8. Edmund, C., and Clemmesen, S.: On Deficiency of A Vitamin and Visual Dysadaptation, London, Oxford University Press, 1936, vol. 1; 1937, vol. 2.

9. Hecht, S., and Mandelbaum, J.: The Relation Between Vitamin A and Dark Adaptation, J. A. M. A. **112**:1911 (May 13) 1939.

10. McCollum, E. V.; Orent-Keiles, E., and Day, H. G.: The Newer Knowledge of Nutrition, ed. 5, New York, The Macmillan Company, 1939, p. 313.

EXPERIMENTAL DATA

Method.—The test is carried out in the following manner: The subject is first dark adapted for ten minutes, remaining in total darkness to compensate for previous conditions of light. A light-proof mask over the eyes is convenient for this purpose and enables one to avoid the difficulty of completely darkening a room. By its use, moreover, one subject can be dark adapted while another is being tested.

At the end of the preliminary dark adaptation the subject is seated at the instrument. Before him, 38 cm. from his eyes, is a panel of translucent glass illuminated from behind, which serves as a source of light of constant intensity for breaking down the retinal pigment. He is asked to focus his eyes on a dark spot on the light panel during three minutes of light adaptation. As the vision is fixed on this spot, the image of the light panel covers a large field in the central part of the retina.

After three minutes the preadaptation light is turned off and two electric clocks, visible only to the operator, are automatically started. In the darkness the subject can see only a pinpoint of light on the panel. Actually, however, below this pinpoint and too dim to be visible at first, the test light is flashing on and off. The subject looks at the pinpoint until he can perceive the test light as it flashes. He then presses a push-button held in his hand, which stops one electric clock. The elapsed time recorded by this clock indicates how rapidly the visual purple has formed after exposure to the preadaptation light.

A second and confirmatory test follows the first. When the subject presses the button, not only is the first recording clock stopped but the flashing test light is automatically dimmed to a second constant value. When his eyes are able to perceive this light of lower intensity, the subject again presses the button, thereby stopping the second electric clock. Thus the regenometer measures two adaptation times.

Hecht and Mandelbaum [9] have set forth certain test conditions that must be known in any valid studies of dark adaptation. The specifications for these conditions in regenometer tests are:

1. The intensity of the "preadaptation" light is 31.2 millilamberts. Its image occupies a retinal field about 44 degrees in diameter.

2. The duration of the preadaptation light is three minutes, a period that was found advisable for this intensity.

3. The test spot is 1.9 cm. in diameter, large enough to be easily perceptible even by persons with impaired visual acuity. Its retinal image is 2 degrees and 52 minutes in diameter. The two intensities of the test spot are 0.011 and 0.0044 microlamberts, respectively.

4. As the vision is centered on the pinpoint of light on the panel, the retinal image of the test light falls approximately 10 degrees above the fovea centralis. This part of the retina contains a high proportion of rods to cones and is accordingly more sensitive to dim light than are locations nearer the fovea.

5. The color of the test light is controlled by a violet filter which transmits only light of wavelength shorter than 475 millimicrons. The retinal rods, the adaptation of which it was considered desirable to test, are much more sensitive to violet light at these low intensities than are the cones. The rods cannot distinguish color, however, so that the test light appears gray to the subject. The test light is blotted out when the subject looks directly at it, as thereby its image falls over the fovea where there are only cones.

6. The test light flashes on intermittently for approximately one-half second, followed by approximately one-half second of darkness.

Procedure.—Ten healthy male students ranging in age from 19 to 24 years were selected from volunteers in various departments of Loyola University at Los Angeles. All were examined by an ophthalmologist for evidence of any visual pathologic condition that might influence the testing.[11]

During experimental periods of forty-two to forty-five days the subjects ingested a diet low in vitamin A. Three alternate menus with estimated vitamin A contents ranging from 300 to 550 U. S. P. units were given, with substitutes allowed for greater palatability. A supplement of vitamin B complex was added to this diet. Dark adaptation tests were made daily except on Sundays and holidays, usually at the same time of day for each subject.

Effect of Diet Low in Vitamin A on Dark Adaptation of Ten College Students

Subject	Age, Years	Height, Cm.	Weight, Kg.	Time Required to See Second Test Light, Min.		Impaired Dark Adaptation† Appeared After	Return to Normal Range Followed Administration of Vitamin A After
				First Eight Days	On Diet Low in Vitamin A*		
D. A.	20	183.0	61.7	2-3	24½	10 days	Over 18 days
J. R.	24	170.0	61.2	1½-2½	23½	17 days	Over 14 days
W. B.	19	180.4	64.8	1-2	6	29 days	10 days
M. D.	19	183.0	70.3	1½-2	5	25 days	2 days
F. M.	20	167.5	73.8	1-2	4½	35 days	§
G. S.	20	180.4	79.3	1-1½	4	32 days	2 days
T. H.	20	178.0	80.3	1½-2½	11½	25 days	7 days
J. H. R.	20	170.0	81.6	1-1½	11½	22 days	Over 12 days
P. G.	21	173.0	83.4	1½-2½	8½	30 days	6 days
J. K.	23	170.0	88.0	1-2	12	31 days	4 days

* Before administration of supplemental vitamin A.

† Over three minute normal range.

§ Given only 500 U. S. P. units of vitamin A supplement daily; showed increased adaptation time of three to six minutes at the end of the experiment on his regular diet.

OBSERVATIONS

As they continued on the diet low in vitamin A, all 10 subjects ultimately showed an increase in the time required to see the test lights. From original values of from one to three minutes, the time required to see the second test light increased to from four to twenty-four minutes with various subjects. This variation may have been due to the fact that some subjects consumed greater quantities of the diet or that utilization of the dietary vitamin A was more efficient in some subjects.

The increase was at first gradual, which suggested a steady depletion of vitamin A reserves. As depletion progressed, the increase became more pronounced. Some of the subjects did not become greatly depleted in the time available for the experiment.

11. Ophthalmologic examinations were made by Dr. Alfred R. Robbins.

There appeared to be a tendency for the tall, thin subjects to show impaired dark adaptation much earlier than did the shorter, heavier ones. While no definite conclusion can be drawn from these data, it would appear that subjects weighing over 73 Kg. did not show adaptation time consistently out of the normal three minute range until the twenty-second to the thirty-fifth days (average, twenty-nine and two-tenths days). Those weighing less than 73 Kg. tested out of the normal three minute range sooner—from the tenth to the twenty-ninth day (average, twenty and two-tenths days).

Unfamiliarity with the test procedure accounted for a few variable adaptation readings at the beginning. That these do not influence the essential results of the test is indicated by the fact that in only 1 instance in the first 80 tests did the time exceed the normal three minute range.

Even in persons whose adaptation time increased tenfold, no other symptoms directly traceable to nutritional deficiencies were observed during the experimental period. All subjects remained in good health and pursued their normal occupations as students. One subject reported a slight itching around the eyes when he was most night blind, and others reported that ocular fatigue was occasionally experienced after the low vitamin A diet had been followed for four or five weeks. However, this period coincided with intensive visual work in studying for examinations and preparing papers at the close of the school term. It is noteworthy that marked dysadaptation was detected long before the appearance of these uncertain symptoms.

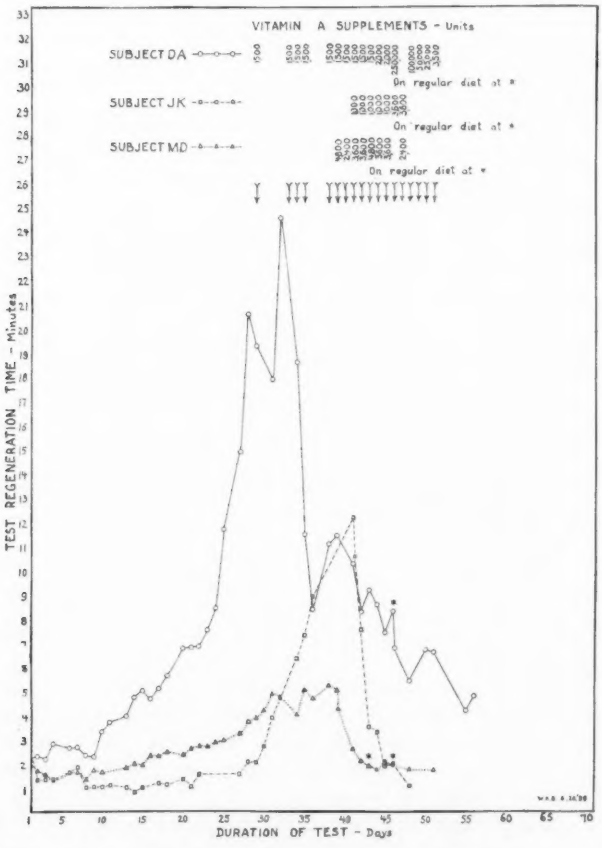
RELATION OF EXPERIMENTAL DYSADAPTATION TO VITAMIN A SUPPLY

All subjects were given vitamin A, some earlier than others because of faster depletion. Tests made the day after the first administration of vitamin A showed a decreased adaptation time except in 1 instance. In this case the subject received only 500 U. S. P. units of supplementary vitamin A. In every case in which a test was repeated within one to three hours after the supplement was given, improved dark adaptation was observed.

The accompanying graph shows in detail the results with 3 subjects, D. A., J. K. and M. D. These 3 were selected from the lowest, the middle and the highest sections of the group. The adaptation time as shown by the second test light has been given, because this measurement is believed to be of greater diagnostic value for latent vitamin A deficiency states than is measurement with the first test light.

Subject D. A. was the first in the group to show impaired dark adaptation. The impairment appeared on the tenth day. His adaptation time increased from a normal value of two or three minutes to nineteen minutes on the twenty-ninth day on the low vitamin A dietary regimen. A single supplement of 1,500 U. S. P.

units of vitamin A reduced the adaptation time, but on the third day following it had increased to twenty-four minutes. When D. A. was given a supplement of 1,500 U. S. P. units of vitamin A for three consecutive days, U. S. P. reference cod liver oil being used as a source, the adaptation time was immediately reduced to eight minutes, as is shown in the chart. Discontinuance of the supplement


VITAMIN A SUPPLEMENTS - Units
SUBJECT DA
On regular diet at *
SUBJECT JK
On regular diet at *
SUBJECT MD
On regular diet at *
TEST REGENERATION TIME - Minutes
DURATION OF TEST - Days

Effect of a diet low in vitamin A on the dark adaptation time of 3 college students. Vitamin A supplementation is indicated by arrows.

for two days brought about an increase to eleven minutes. Thereafter the daily administration of 1,500 U. S. P. units brought the period back to eight and one-half minutes. This was still above his normal adaptation value. Two thousand U. S. P. units of vitamin A for two days brought about slight improvement.

The effect of massive doses of vitamin A was observed by feeding 25,000 to 250,000 U. S. P. units in the form of cod liver oil concentrate. These doses failed

to decrease the adaptation time to a greater degree than did the much smaller doses previously used. Thereafter his normal diet was followed for four days, and his adaptation time was reduced to four to five minutes. Unfortunately, the experiment had to be terminated before his normal values could be regained.

Subject J. K. showed impaired dark adaptation on the thirty-first day. By the forty-first day the adaptation time had reached twelve minutes. He was given 1,000 U. S. P. units of vitamin A as U. S. P. reference oil, and his adaptation time decreased somewhat within a few hours. After four daily doses of 1,000 U. S. P. units of vitamin A, his adaptation time decreased from twelve to two minutes. This amounts to about 17 units per kilogram of body weight (1,000 units in the supplement and 500 units in the diet). After two days of his regular diet plus 3,600 U. S. P. units of vitamin A the time further decreased to one minute.

M. D., as is shown in the chart, showed an increase in adaptation time above the normal on the twenty-fifth day. At thirty-nine days his adaptation time was five minutes. He was given a daily supplement of 3,600 U. S. P. units of vitamin A, and within four days his adaptation time decreased to two minutes. With this supplement and his normal diet he remained at this level for eight successive days.

T. H. first showed impaired dark adaptation after twenty-five days on the low vitamin A dietary regimen. On the forty-first day his adaptation time was eleven and one-half minutes. After he had received 500 U. S. P. units of vitamin A supplement daily for three days, the time decreased to five and one-half minutes. When he returned to his regular dietary regimen, plus about 2,400 U. S. P. units of vitamin A daily, it took four additional days for his adaptation time to return to its normal value.

J. H. R. had an adaptation time of eleven minutes after receiving the low vitamin A diet for thirty-nine days. He received 3,600 U. S. P. units of vitamin A daily. After four days, during which his adaptation time decreased from eleven to eight minutes, he returned to his regular dietary regimen but continued the supplement. His adaptation had not returned to its normal value after eight more days.

P. G. received 500 U. S. P. units of vitamin A daily after his adaptation time had reached eight minutes. After three days the time decreased to four and one-half minutes. A massive dose of 125,000 U. S. P. units of vitamin A improved his testing time only thirty-eight seconds at four hours after administration. His values were normal after six days of supplementation.

W. B. received 500 U. S. P. units of vitamin A supplement daily when (on the forty-first day of his low vitamin A diet) his adaptation time had increased to five and one-half minutes. This was sufficient to cause a temporary decrease in the adaptation time but not sufficient to maintain it. Five days of regular dietary regimen and supplementation with vitamin A brought him within the normal three minute range.

These data indicate the following conclusions: 1. The rate of depletion of stored vitamin A is variable. 2. Depletion, once initiated, proceeds relatively fast. 3. On the basis of these results an adaptation time of one to three minutes for the second test point may be considered normal. It was observed that normal subjects perceive the second test light within one minute of the first, but as depletion proceeds a pronounced spread occurs between the two adaptation states. These results offer confirmatory evidence of the deficiency state. 4. After administration of vitamin A there is at first a rapid utilization by the retina, as indicated by a rapid decrease in the adaptation time. However, continued administration of a vitamin A supplement produced improvement at a less rapid rate.

COMPARISON OF REGENOMETER WITH BIOPHOTOMETER

Dark adaptation tests were made on all subjects with the biophotometer at the time when most of the subjects showed the greatest adaptation times with the regenometer.

The biophotometer readings for J. R. were well within the normal range when the regenometer gave an adaptation time of sixteen minutes, more than five times greater than normal. P. G. gave a low biophotometer reading when his testing time of six minutes indicated only a mild deficiency by the regenometer.

Most of the subjects were found to be within the normal range by the biophotometer. This would seem to suggest a greater sensitivity of the regenometer in the detection of early states of vitamin A deficiency.

COMMENT

The average depletion time for 6 subjects weighing over 73 Kg. was twenty-nine and two-tenths days. The average depletion time for 4 subjects weighing under 73 Kg. was much less (twenty and two-tenths days). Whether a lower store of vitamin A, higher daily requirements or poorer utilization of carotene in the diet was responsible for more rapid depletion of the subjects of lower weight cannot be known from these data.

In harmony with the observations of Booher, Callison and Hewston,[12] it is evident that in the return to the normal state there is at first a rapid, though suboptimal, mobilization of vitamin A in the retina. Then follows a slower improvement, seemingly uninfluenced by a greatly increased vitamin A intake. A supplement of only 500 U. S. P. units of vitamin A per day produced rapidly improved dark adaptation in 2 subjects.

For subject D. A., a daily intake of approximately 2,000 U. S. P. units of vitamin A (1,500 units in the supplement and 500 units in the diet) served to produce improved dark adaptation. This is an intake of approximately 32 units per kilogram of body weight for this subject and hence falls well within the range of requirements suggested by Booher and her collaborators.[12] This intake was fairly close to the twenty-four hour requirement, owing to the fact that suspension of the supplement for three days (thirtieth to thirty-second inclusive) caused a pronounced increase in the dark adaptation time. The same observation was made when the supplement was suspended on the thirty-sixth to the thirty-seventh day. The fact that this subject remained in the

12. Booher, L. E.; Callison, E. C., and Hewston, E. M.: An Experimental Determination of the Minimum Vitamin A Requirements of Normal Adults, J. Nutrition **17**:317, 1939.

normal range for only the first ten days of the experiment indicates a previous suboptimal vitamin A intake, a low storage or an increased requirement.

The feeding of massive doses of vitamin A, up to 250,000 U. S. P. units, was not proportionately more effective than much smaller amounts (1,500 to 3,600 U. S. P. units per day) in improving experimental night blindness caused by vitamin A deficiency.

No clinical symptoms of vitamin A deficiency were observed during the course of the experiments.

Relatively smooth curves even with the large number of experimental determinations indicate that the experimental errors were small.

Unfortunately these studies were carried out late in the college year, and the subjects could not be retained for study as long as was desirable. A longer time than was available and a greater intake of vitamin A were evidently required for a complete return of 4 subjects to normal dark adaptation.

SUMMARY

A simple and sensitive test for detecting impaired dark adaptation is described. The course of vitamin A depletion of 10 college students on diets low in vitamin A was followed with this technic. All the subjects required a longer time to see a test light of constant intensity as depletion progressed and showed improvement as vitamin A supplements were administered. Individual variations in dark dysadaptation were observed and are discussed.

PROTAMINE ZINC INSULIN: A CLINICAL STUDY

REPORT OF A GROUP OF DIABETIC PATIENTS IN WHOSE CASES GLYCOSURIA WAS DISREGARDED FOR ONE YEAR

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The purpose of this communication is to present our observations on a group of diabetic patients who have been observed for a year or more during treatment with one daily dose of protamine zinc insulin. Furthermore, we plan to discuss briefly our routine therapy as well as to review the events which contributed to the adoption of the principles presented in this publication.

Protamine zinc insulin has been used in the treatment of diabetes mellitus for nearly four years. True, the original compound as prepared by Hagedorn [1] has undergone slight modifications, but basically the product is still regular insulin which has been mixed with protamine (a simple protein) with small quantities of zinc added to the compound. The resulting mixture, a milky suspension, is much less soluble, and is therefore more slowly absorbed in the subcutaneous tissues, than the clear soluble insulin hydrochloride discovered by Banting and Best.[2]

Since protamine zinc insulin became commercially available, in 1937, thousands of patients with diabetes mellitus have been treated with it, and certain definite clinical facts have been established by numerous clinicians in the United States and abroad. All have agreed that protamine zinc insulin acts more slowly than regular insulin, that during the first three to six hours it shows little, if any, activity as judged by its effect on the blood sugar, that its pharmacologic effect continues for at least twenty-four hours with moderate doses and longer with larger ones, that reactions, though less frequent, are characterized by suddenness of onset and are severe and prolonged and that patients have reported a definite subjective improvement.

From the New York Hospital and the Department of Medicine, Cornell University Medical College.

1. Hagedorn, H. C.; Norman Jensen, B.; Krarup, N. B., and Wodstrup, I.: Protamine Insulinate, J. A. M. A. **106**:177 (Jan. 18) 1936.

2. Banting, F. G., and Best, C. H.: J. Lab. & Clin. Med. **7**:251, 1922.

We were particularly attracted to protamine zinc insulin because of the possibility of using a single dose of the preparation instead of the customary two, three or even four daily injections necessary with regular insulin. However, the use of a single dose of protamine zinc insulin proved disappointing with our patients with moderately severe and severe diabetes mellitus. With the diets employed at our clinic (200 to 250 Gm. of carbohydrate) our patients revealed either intermittent or continuous heavy glycosuria. When we attempted to treat the glycosuria by increasing the dose of protamine zinc insulin, the urine became free from sugar but the patient suffered from insulin reactions, at times of alarming severity. To obtain the "physiologic" or "ideal" regulation, that is, maintenance of the urine free from sugar, we attempted various dietary divisions and also withheld the easily absorbable carbohydrates as suggested by Pollack,[3] but our efforts were fruitless. All of these observations were on ambulatory patients of the clinic. On numerous occasions we observed that some of the patients, though they received one dose of protamine zinc insulin a day and revealed marked glycosuria, enjoyed good health, were in fine spirits, maintained their weight and were remarkably free from any symptoms of diabetes mellitus. We could not help being profoundly impressed and influenced by these observations, and it occurred to us that perhaps the criteria for satisfactory treatment of diabetes would have to be reevaluated. Was it possible that with protamine zinc insulin such fundamental therapeutic criteria as urine free from sugar and a normal value for blood sugar might stand revision? Was it at all likely that the patient's actual condition, that is, his weight, his ability to "carry on," his well-being and his psychic outlook, might be a more important guide than the height of the concentration of blood sugar and the glycosuria? How safe was it to allow our patients to excrete large quantities of dextrose over long periods? Would they have ketosis on this regimen of one single dose of insulin with continuous glycosuria? The question of the effect of continuous hyperglycemia and glycosuria on the frequency and severity of infections was also a consideration. With constant teaching by physicians of great experience in the field of diabetes mellitus that a normal level of blood sugar and urine free from sugar were the absolute essentials for satisfactory therapy, it was extremely difficult for us to reconcile this orthodox view with our clinical observations, namely, that a patient could feel perfectly well and be free from symptoms while revealing so-called poor control as evidenced by hyperglycemia and glycosuria. It was our feeling that an answer to our question would be more satisfactorily obtained with hospitalized patients.

3. Pollack, H.: J. Mt. Sinai Hosp. **4**:437, 1938.

whom we could observe with great care and detail. We, therefore, admitted 2 patients with severe diabetes to the metabolism ward for study. The results of this work have been published in detail elsewhere.[4] Briefly, our observations were that these patients, who received one dose of protamine zinc insulin daily as well as a diet of 1,640 calories composed of 75 Gm. of protein, 60 Gm. of fat and 200 Gm. of carbohydrate, could maintain their weight, be in nitrogen equilibrium, excrete no ketone bodies in the urine and be absolutely free from symptoms even though they excreted an average of 100 Gm. of dextrose a day over one experimental thirty day period and presented consistently high values for blood sugar. These patients were observed for fifty and sixty days each, and from the data obtained we postulated as a working hypothesis the following criteria for satisfactory treatment of diabetes mellitus with protamine zinc insulin

1. Maintenance of weight
2. Absence of ketone bodies in the urine
3. Freedom from the following symptoms:
   a. Thirst
   b. Polyuria
   c. Frequency of urination
   d. Hunger
   e. Weakness; fatigue
   f. Polyphagia
   g. Pruritus (limited to the genitalia, chiefly in females)
   h. Visual disturbances

In arriving at these conclusions we felt that it was the *utilization* and not the excretion of carbohydrates which was of prime importance, and that with patients treated as described the glycosuria was not an undesirable feature, as it protected the patient from reactions. This view has been substantiated in principle by recent publications,[5] the major difference being a quantitative one. Even the most conservative observers feel that with the use of protamine zinc insulin glycosuria is compatible with good therapy. Some permit excretion of only 10 per cent of the carbohydrate intake; others, as much as 20 per cent.

Employing the single dose method and using the criteria outlined as guides for satisfactory treatment, we have treated 84 patients. All

4. Tolstoi, E., and Weber, F. C., Jr.: Protamine Zinc Insulin: Metabolic Study; Treatment in Two Cases of Severe Diabetes by Equally and Unequally Divided Diets, with Comments on Criteria for Treatment, Arch. Int. Med. **64**:91 (July) 1939.

5. Joslin, E. P.: Mil. Surgeon **82**:1, 1938. White, P.: South. M. J. **31**:15, 1938. Protamine Insulin and Diet in Diabetes Mellitus, editorial, Ann. Int. Med. **11**:2048, 1938.

the observations were carried out in the outpatient department, and consequently all of our patients were ambulatory.

We did not even attempt to "desugarize" our patients. Of course, if the patient maintained his weight on the prescribed diet and with the single dose of protamine zinc insulin revealed no glycosuria, the therapy was continued. However, if the patient continued to excrete sugar and revealed no evidences of loss of weight or ketosis, no effort was made to obtain a specimen free from sugar by altering the diet or the dose of insulin or both. There were 27 patients in whose cases such observations were made. All of these revealed almost continuous glycosuria during a year or longer. The glycosuria was determined qualitatively only. The group was composed of the average type of clinic patient, whose health was absolutely essential for livelihood. The diet was never weighed. It was always calculated on the basis of household measures and at best was only an approximation. All of the patients were instructed to take a glass of milk and three crackers or a slice of bread at bedtime. They were requested to test their urine for purposes of record and were advised not to be upset if the analysis revealed sugar. They were cautioned, however, that if thirst, frequency of urination or unusual hunger appeared they should report to us at the clinic. Usually when the patient arrived his weight and pulse rate were recorded. A portion of a twenty-four hour specimen of urine from the preceding day was then examined by the nurse in charge, and the findings (chiefly for dextrose and acetone) were entered on the chart. The patient then consulted with the dietitian, and an approximate estimate was made of the food intake of the past twenty-four hours. During these consultations the patient was given an opportunity to ask all sorts of questions in connection with his diet. In other words, the consultations with the dietition were not limited to analyses of the intake but were of educational value. After all these preliminaries the patient would see the physician, who noted the patient's weight and the results of the tests for acetone and then questioned the patient concerning symptoms. If our criteria for satisfactory treatment were fulfilled, that is, if there was no loss of weight, no symptoms and no ketonuria, no therapeutic changes were made even though 4 plus glycosuria was present. If, however, there were a loss of weight and glycosuria, the amount of protamine zinc insulin was increased at frequent intervals until there was a gain of weight. For example, if the patient had been receiving 35 units of protamine zinc insulin and with this dosage and a diet which we felt was calorically ample for him was revealing glycosuria and losing weight, the dose of insulin was increased to 45, 50 or even 60 units, until he ceased to lose weight or gained. As soon as we could demonstrate a gain or even maintenance of weight the glycosuria was disre-

garded. No determinations of the concentration of blood sugar were made systematically in these cases.

Very rarely because of a slight cold and also at times without any obvious cause a slight trace of acetone was found in the urine. This was never of serious consequence. It was treated by the administration of salt tablets, 1 Gm. (two 0.5 Gm. pellets) every two hours, with a glass of water for each dose. In addition, hot salty broths were recommended. Usually the acetone disappeared, but when it persisted or increased one or two small doses of regular insulin usually sufficed to render the urine free from acetone. Of the 84 patients observed, only 27 revealed glycosuria almost constantly present during the period of treatment, that is, a year or more. The remaining group showed only occasional glycosuria and revealed no clinical symptoms. Since this is acceptable by all as satisfactory control, no comment on this group is necessary. However, we wish to present in some detail the records of the 27 patients in whose urine sugar was almost constantly present for over twelve months.

An examination of the tabulated data shows that there were 10 male and 17 female patients, whose ages varied from 15 to 71 years. The diabetes was moderately severe and severe, and its duration was from one to fourteen years. The dose of insulin varied from 10 to 60 units, with an average of about 25. The carbohydrate fraction of the diet was 150 Gm. lowest and 250 Gm. highest. All of the patients revealed variable glycosuria, from zero to 4 plus with the latter a more frequent finding. Five of the patients showed 4 plus glycosuria [6] at every examination. Nineteen of the 27 patients gained weight; the minimum gain was 0.2 Kg. and the maximum 14.4 Kg. Six lost weight (maximum, 5.4 Kg.; minimum, 0.2 Kg.). Two patients neither gained nor lost. None of the patients presented any symptoms of diabetes even though glycosuria was present. There were no unusual infections. The common cold was seen in several of this group, but at no time was it incapacitating. Only 1 of this group revealed occasional acetonuria. This was observed whenever the patient had a cold. It was never severe and did not require any other treatment than the salt tablets, fluid and one or two additional doses of regular insulin.

We then reviewed the records of the patients who lost an appreciable amount of weight while under observation. We noted that their weight did not always continue to fall. There were oscillations throughout the year, and we have merely presented their weights at the beginning and end of the period of protamine zinc insulin therapy. Brief summaries of their records are given (for further data, see table).

6. As determined by red or yellow staining with Benedict's solution.

Data on Twenty-Seven Patients with Diabetes Mellitus Treated with Protamine Zinc Insulin

Case	Sex	Age	Duration of Diabetes		Duration of Treatment with Protamine Zinc Insulin		Number of Units	Approximate Diet, Gm.			Glycosuria (Qualitative)	Weight		Change in Weight, Kg.	Symptoms During Treatment
			Yrs.	Mos.	Yrs.	Mos.		Protein	Fat	Carbohydrate		Before Protamine Zinc Insulin	After Protamine Zinc Insulin		
1	F	17	2	..	1	10	25-60	70	60	225	4 plus continuously*	47.3	54.4	+ 7.1	None
2	M	15	2½	..	2	1	14-16	100	110	250	0-4 plus	48.0	56.7	+ 8.7	None
3	F	56	2½	..	1	2	25-20	75	50	170	2-4 plus	57.1	59.9	+ 2.8	Frequent colds last winter
4	F	61	7	..	1	3	35-45	70	70	175	1-4 plus	58.7	56.6	— 2.1	Teeth extracted; no difficulty
5	F	58	7	..	1	4	40	80	70	200	0-4 plus	46.3	47.9	+ 1.6	None
6	F	19	7	..	3	..	50	75	80	150	4 plus continuously	48.2	51.0	+ 2.8	None
7	M	51	1	4	1	4	30-20	70	60	150	0-2 plus	66.0	70.0	+ 4.0	None
8	M	17	3	10	3	10	15-20	80	90	220	4 plus continuously	44.5	53.6	+ 9.1	None
9	F	58	2	10	1	3	25	60	90	195	0-2 plus rare 4 plus	53.7	58.5	+ 4.8	None
10	F	48	10	..	1	5	40-45	60	60	225	2-4 plus	51.2	56.0	+ 4.8	None
11	F	49	11	..	1	6	30-40	70	50	140	1-4 plus	58.8	56.4	— 2.4	Occasional headaches for 6 years
12	M	41	4½	..	1	6	20-30	70	70	200	4 plus continuously	61.1	61.0	± 0	Toothache and extraction; no complications
13	M	30	2	..	1	7	20-29	90	120	250	0-3 plus	63.8	64.6	+ 0.8	Occasional reactions
14	F	47	9	..	1	..	25-30	65	70	200	4 plus continuously	63.0	62.8	— 0.2	None
15	F	28	5	..	1	8	50	75	115	125	4 plus	60.0	58.0	— 2.0	None
16	F	68	7	..	1	1	25-20	80	65	200	0-2 plus	61.1	75.5	+14.4	None
17	M	32	3	10	1	4	25-20	70	60	200	1-4 plus	60.4	60.0	— 0.4	None
18	M	61	2½	..	2	..	10	90	60	250	0-4 plus	74.7	69.3	— 5.4	None
19	M	28	1	4	1	1	30-40	90	90	250	0-4 plus	60.1	64.4	+ 4.3	None
20	F	30	2	10	1	7	30	70	70	150	0-4 plus	46.3	52.0	+ 5.7	None
21	F	46	6	..	1	4	25	70	80	200	1-4 plus	48.2	50.0	+ 1.8	None
22	M	71	14	..	1	..	20-35	70	50	175	0-4 plus	68.7	69.9	+ 0.3	Pain on walking
23	F	64	4	..	1	1	15	70	50	175	0-3 plus	44.0	44.3	+ 0.3	None
24	F	61	4	..	1	4	20	70	60	150	0-2 plus	66.9	70.6	+ 3.7	None
25	M	35	2	10	1	..	20	100	80	250	0-3 plus	69.0	75.2	+ 6.2	None
26	F	16	1	..	1	..	40	70	65	250	4 plus continuously	48.2	51.5	+ 2.7	None
27	F	24	5	..	2	..	25-55	80	75	250	2-4 plus	70.0	70.0	+ 0	Occasional colds

* Occasional acetone.

REPORT OF CASES

CASE 4 (loss of 2.1 Kg.).—J. C. had severe diabetes. When a single daily dose of 35 units of protamine zinc insulin was started, in June 1938, she weighed 58.7 Kg. Six months later she weighed 56.9 Kg. At this point the diet was increased, and her weight two months later rose to 58.5 Kg. Later, during the summer months, she lost 1 Kg. because of the heat and a poor appetite. She had some dental extractions during this period, with excellent healing. Her present weight is 56.6 Kg.

CASE 11 (loss of 2.4 Kg.).—F. B. had been taking 30 units of protamine zinc insulin daily, and on admission to the clinic, November 1938, she weighed 58.8 Kg. She has schooled herself in eating less than is prescribed, but at one period (May 1939) when she did enjoy her full diet her weight rose to 60 Kg.

CASE 15 (loss of 2 Kg.).—F. H. has been studied in detail in the metabolic service, and her loss of weight was noted while she was in the hospital on a subcaloric diet of 1,650 calories. On admission to the hospital she weighed 60 Kg. On discharge her weight was 58 Kg. Seven months later her weight was 59 Kg.

CASE 18 (loss of 5.4 Kg.).—A mildly diabetic patient has been receiving 10 units of protamine zinc insulin. His diet and insulin dosage have been very irregular, the latter having been omitted occasionally for seven to ten day periods.

COMMENT

From the study of this group of 84 diabetic patients in the outpatient department who for one year have received one daily injection of insulin and in whose cases no particular effort was made to maintain the urine free from sugar, it is seen that only 27 revealed persistent glycosuria throughout the period of observation. These 27 patients were in good health, and furthermore they were in a state of social and economic usefulness. Not only did the majority of them maintain their weight, but some gained weight, even though heavy glycosuria was almost continuously present. There were no complaints or symptoms at any time associated with the glycosuria, and infections were no more frequent in this group than in the group whose urine was mostly free from sugar. All the patients in this group enjoyed much more freedom, as there appeared no necessity for careful dietary measurements, and it was not necessary for them to carry with them their syringe and insulin. They administered the insulin to themselves in the morning and then put the equipment away until the following day. Thus, the patients were not singled out as a group apart from their fellow men, and their habits of living approximated the normal ones.

At this point it may be argued that since we direct our efforts toward making the lives of this group normal as to living habits, why not extend our efforts in the direction of "physiologic normality" so far as the diabetes is concerned, that is, toward obtaining urine free of sugar and possibly a normal level of blood sugar, as these objectives

have been considered synonymous with proper utilization of the carbohydrates? This may be sound, but what evidence is there to show that with protamine zinc insulin such utilization of carbohydrates does not take place in spite of hyperglycemia and glycosuria? None whatever. Glycosuria has been such a dominant component in the study of the treatment of diabetes that the more important factor of utilization has been almost totally ignored, although it was emphasized long ago by the Russell Sage group of investigators.[7]

In 1914, Allen and DuBois [7b] presented calorimetric studies on diabetic patients showing that the diabetic person can and does utilize carbohydrate in the presence of hyperglycemia and glycosuria. Some of their patients showed a maximum utilization of carbohydrate, as judged by the respiratory quotient, when the carbohydrate fraction of the diet was at its maximum and the glycosuria at its highest level. For a short period, while these patients were observed with the calorimeter, they revealed a capacity to utilize carbohydrate approaching the physiologic ideal. Additional evidence that such utilization of carbohydrate takes place even in the presence of the most severe diabetes has been published by Gephart, Aub, DuBois and Lusk.[7a] The experimental subject, Cyril K., with very severe diabetes, was able to derive 62 per cent of his total calories from carbohydrate when given a diet of 60 Gm. of protein, 60 Gm. of fat and 252 Gm. of carbohydrate, a most unorthodox diet for that era but evidently effective in promoting the utilization of carbohydrate. The authors stated: "This astonishing result shows that Cyril K., who two months before had been completely diabetic, was now able to derive two thirds of his basal requirement for energy from the oxidation of carbohydrate." This group of observers established with certainty that for short periods, at least, the diabetic patient, irrespective of the severity of the disorder, is capable of utilizing carbohydrate. Unfortunately the process did not continue. Today one can prolong this utilization of carbohydrates by means of insulin, so that in place of the short duration of the so-called physiologic ideal, utilization, a longer duration is produced. If this postulate is accepted, hyperglycemia and glycosuria must be of secondary importance. The most important and physiologic basis for satisfactory treatment, therefore, is *not how much sugar is excreted but how much is metabolized.* Recently, Bridge and Winter [8] have studied this question of carbohydrate metabolism while noting the effect of insulin on diabetic patients. They found no correlation whatever between the height of the

7. (*a*) Gephart, F. C.; Aub, J. C.; DuBois, E. F., and Lusk, G.: Metabolism in Three Unusual Cases of Diabetes, Arch. Int. Med. **19**:908 (May) 1917. (*b*) Allen, F. M., and DuBois, E. F.: Metabolism and Treatment in Diabetes, ibid. **17**:1010 (June) 1916.

8. Bridge, E. M., and Winter, E. A.: Bull. Johns Hopkins Hosp. **44**:257, 1939.

value for blood sugar and the respiratory quotient in cases of diabetes treated with insulin. They reported also that with wide fluctuations from the hyperglycemic to the hypoglycemic level there was no indication that carbohydrate was being utilized at different rates. In other words, these investigators have clearly demonstrated that in an insulin-treated diabetic person carbohydrate is utilized in the presence of hyperglycemia and sequential glycosuria. They concluded that in view of these important findings neither the value for blood sugar nor the degree of glycosuria is an adequate criterion for the regulation of diabetes. Their conclusion is particularly applicable to patients treated with protamine zinc insulin, in whom carbohydrate utilization can be maintained as long as the insulin is active.

From the clinical side we have gathered evidence which has led us to similar conclusions. We feel that if a state of carbohydrate utilization can be maintained in the diabetic person (and this is readily accomplished by the use of protamine zinc insulin) a physiologic state has been created, and furthermore it is our feeling that the guiding principles for such a status in the presence of glycosuria and hyperglycemia are (1) maintenance of weight, (2) freedom from symptoms of diabetes and (3) absence of ketone bodies in the urine.

SUMMARY AND CONCLUSIONS

Eighty-four patients with diabetes mellitus were treated with one daily dose of protamine zinc insulin. No particular effort was made to maintain the urine free from sugar, and yet only 27 patients revealed almost continuous glycosuria throughout the period of study (one year). The results in this group are presented in detail. Briefly, the great majority of them maintained their weight, and many gained. None presented any symptoms of diabetes mellitus, and only 1 revealed mild acetonuria (on very rare occasions). Their diets were not weighed. The incidence of infections was no greater in this group than in other patients. Guiding principles for the treatment of diabetes mellitus with protamine zinc insulin are proposed. These are based on clinical and experimental studies. The facts are presented and the theoretic concepts discussed.

EVALUATION OF VITAMIN B THERAPY FOR DIABETES

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Several investigators have published results indicating a definite value of vitamin therapy for diabetes.[1] Careful survey of their publications, however, reveals lack of a proper period of control of diabetes before institution of the therapeutic tests. In few of the case histories described are there evidences of stability in the diabetic state before the special therapy was initiated. Thus it is always doubtful whether the improvement observed was due to the vitamins given or to the continued regulation of dietary and insulin needs. Diabetic patients were often given vitamin preparations while they were still improving under previously instituted dietary and insulin regimens, and any further improvement was credited to the vitamin.

Good results have been claimed for administration of thiamine and ascorbic acid to diabetic persons, even though most diabetic diets are adequate in these two substances. Since these claims seem to have been based in most instances on improperly controlled patients, we have undertaken a similar study on patients well standardized for six to eighteen months prior to the period of administration of vitamins. Under such conditions of adequate control of the patient thiamine and riboflavin are found to produce no noticeable alteration in the diabetic state, except for an amelioration of neuritic pain by thiamine.

1. Vorhaus, M. G.; Williams, R. R., and Waterman, R. E.: Studies on Crystalline Vitamin B_1: Observations in Diabetes, Am. J. Digest. Dis. & Nutrition **2**: 541-554, 1935. Dienst, C.: Ist der Diabetes durch die Vitamine B und C beeinflussbar? Deutsche med. Wchnschr. **65**:710-715, 1939. Pfleger, R., and Scholl, F.: Diabetes und Vitamin C, Wien. Arch. f. inn. Med. **31**:219-230, 1937.

METHODS

A group of 25 outpatients from the diabetic clinic of the Cincinnati General Hospital were selected as clinical test material for study. All were considered to have moderate to severe diabetes. Their ages varied from 18 to 66 years. All had been adequately controlled for many months before this period of study began, except 2 patients with neuritis, whose control treatment began with, or shortly before, this study. In no case did serious infection complicate the study. Except for an increase in the 2 cases of neuritis, the dietary values were held constant throughout the period of study at the same level that had prevailed for months previously. Changes in the insulin dosage were few and are recorded in table 1. The weight of each patient was recorded at the beginning of the study and watched

TABLE 1.—*Thiamine: Moderate Doses*

				Weight, Pounds			Insulin, Units		Thiamine		Symptoms Present		Symptoms Improved	
Patient	No.	Age	Sex	Before	After	Diet	Beginning	End	Daily Dose, Mg.	Weeks Given	Specific	Nonspecific	Specific	Nonspecific
B. A.	1	56	M	144	143	See	20	30	3.3	16	+	+	++	++
W. C.	2	24	M	126	127	table	35*	35*	3.3	16	0	0	0	0
F. N.	3	59	F	127	126	5	32*	32*	3.3	14	0	+	0	++
X. C.	4	52	M	151	140		50*	50*	3.3	16	0	0	0	0
I. J.	5	54	F	103	119		50*	40*	3.3	16	+	+	++++	++++
R. B.	6	57	M	115	119		50*	45*	3.3	8	0	+	0	+, —
I. S.	7	56	F	132	131		18*	15*	3.3	14	0	+	0	+
L. B.	8	53	M	158	154		30	30	3.3	16	0	+	0	++
C. B.	9	20	F	148	153		53*	56*	3.3	16	0	0	0	0
J. N.	10	31	M	125	126		45*	45*	3.3	16	0	+	0	0
J. M.	11	18	M	145	146		45*	45*	3.3	16	0	0	0	0
T. R.	12	54	F	168	170		50*	50*	3.3	16	0	0	0	0
J. S.	13	48	M	143	142		50	44	3.3	8	0	+	0	+, —
S. P.	14	66	F	124	122		15	15	3.3	16	0	+	0	0
G. A.	15	57	F	122	127		30*	30*	3.3	16	0	+	0	0
L. B.	16	37	F	122	123		52†	52†	3.3	14	0	+	0	++
R. H.	17	32	M	150	146		40†	40†	3.3	14	0	+	0	++
J. D.	18	20	M	121	125		50*	50*	3.3	12	0	0	0	0
N. R.	19	40	F	120	120		15*	30*	3.3	16	0	0	0	0
J. M.	20	46	M	156	158		30	30	3.3	16	0	+	0	0

* Protamine zinc insulin.
† Crystalline zinc insulin.

throughout the period. Control of the diabetic state in these patients was determined by examination of the usual four daily specimens of urine for sugar. During the entire period of study only 2 patients showed occasionally more than a 1 plus reaction for sugar in the urine, the others usually excreting no sugar or only a trace.

In order to leave no doubt that the patients received the full effect of all thiamine prescribed, thiamine chloride solution (10 mg. per cubic centimeter) was added to the insulin used, and the patients were advised as to the proper correction in dosage volume to cover their insulin needs. No apparent reaction between the insulin and the thiamine occurred,[2] and the blood sugar-lowering effect of the insulin remained unaltered (as carefully tested on 3 patients). Riboflavin was administered orally, 2 mg. daily.

2. The manufacturer states: "It is our opinion that neither the potency of insulin nor vitamin B_1 is appreciably affected when the two are together in solution."

RESULTS

Thiamine Therapy.—The thiamine-insulin mixture was given to 20 well regulated diabetic patients in amounts sufficient to cover their insulin needs and to supply 3.3 mg. of thiamine daily. After eight, twelve and sixteen weeks respectively of this regimen, the dose of thiamine was increased to 5 mg. daily for 3 of these same patients, and to 8.3 mg. for 1 other after eight weeks. Table 1 indicates the details of diet, the insulin and thiamine dosage and the therapeutic results obtained with these 20 patients during the period of thiamine therapy.

No effects of the thiamine were observed either in the general nutritional state of the patients or in their dietary or insulin needs for proper control of the diabetic state. One patient gained 16 pounds (7.3 Kg.) in weight; another lost 11 pounds (5 Kg.). The greatest reduction in the dose of insulin during the sixteen week period was a reduction of 10 units daily for 1 patient, who had been brought under control only shortly before beginning the thiamine therapy. An increase of 15 units for another patient was necessary to cover a dietary addition. A third patient, who was sometimes careless as to food intake, required an increase of 10 units during the period. All 20 patients were maintained at a control level, so that occasional traces of sugar appeared in the urine but insulin reactions were absent. It seems safe to say, therefore, that thiamine therapy within reasonable limits does not appreciably alter the diabetic state of previously well controlled patients.

An attempt to evaluate the effects of thiamine on the general symptoms of each patient is difficult. Except in 2 patients, no specific symptoms were present. Several patients had various complaints before and during the study, such as lack of appetite, ease of fatigue, lack of "pep" and indefinite pains here and there. Of the 11 patients with these indefinite complaints, 6 showed no change, and 5 reported rather definite improvement. The appetite of these 5 was better; they did not tire so easily and felt generally stronger. The thiamine solution was withheld from these 5 patients without their knowledge, and 3 of them continued to show the same improvement, while 2 noted a slight reduction in their feeling of improvement. Two of the group reported marked improvement after one week of the added thiamine therapy; however, in three more weeks the feeling of improvement had changed to the opposite. Both asked to have administration of thiamine discontinued. There were, however, 2 patients with definite diabetic neuritis. One of these was the newly controlled patient, and the other was the least cooperative subject. Both showed definite improvement of their neuritic symptoms, the former being completely relieved within about three months and the latter much improved.

Table 2 shows the results of large doses of thiamine. The patients had already received 3.3 mg. of thiamine and had not improved. Doses of 5 mg. were then given to 3 and a dose of 8.3 mg. to the other. There was a loss of weight in 1, which was probably due to the fact that he reduced his own diet. The dose of insulin was reduced 5 units for

TABLE 2.—*Thiamine: Large Doses*

				Weight, Pounds			Insulin, Units		Thiamine		Symptoms Present		Symptoms Improved	
Patient	No.	Age	Sex	Before	After	Diet	Beginning	End	Daily Dose, Mg.	Weeks Given	Specific	Nonspecific	Specific	Nonspecific
J. M.	11	18	M	146	146	See	45*	45*	5	8	0	0	0	0
J. S.	15	48	M	142	142	table	44	44	8.3	8	0	+	0	0
R. B.	6	57	M	119	107	5	45*	40*	5	8	0	+	0	0
J. N.	10	31	M	126	126		45*	45*	5	8	0	+	0	0

* Protamine zinc insulin.

TABLE 3.—*Riboflavin*

				Weight, Pounds			Insulin, Units		Riboflavin		Symptoms Present		Symptoms Improved	
Patient	No.	Age	Sex	Before	After	Diet	Beginning	End	Daily Dose, Mg.	Weeks Given	Specific	Nonspecific	Specific	Nonspecific
							A							
I. J.	5	54	F	119	122	See	20*	20*	2	8	0	0	0	0
Z. J.	21	57	M	138	138	table	42*	40*	2	8	0	0	+	0
R. C.	22	34	M	174	173	5	60†	60†	2	8	0	0	0	0
A. M.	23	29	M	139	135		42*	42*	2	8	0	0	0	0
G. A.	15	57	F	127	126		30*	30*	2	8	0	+	0	0
W. R.	24	58	M	117	117		40	40	2	8	0	+	0	0
J. S.	13	48	M	142	143		44	44	2	8	0	+	0	+
R. B.	6	57	M	107	107		40*	40*	2	8	0	+	0	+
C. P.	25	64	F	103	103		8*	8*	2	8	0	+	0	0
F. N.	3	59	F	126	126		32*	32*	2	8	0	0	0	0
							B							
G. A.	15	57	F	126	124		30*	30*	2‡	8	0	+	0	0

* Protamine zinc insulin.
† Crystalline zinc insulin.
‡ 3.3 mg. of thiamine given with the 2 mg. of riboflavin daily.

the same patient, the reason for this being the reduction in diet. The others showed no change in weight, diet or insulin need, and none of the 4 reported any change in general feeling. It seems evident that even with large doses of thiamine chloride administered to well controlled diabetic patients the diabetes is not appreciably changed.

Riboflavin Therapy.—In table 3 are shown the effects of riboflavin administered to 10 of the 25 diabetic patients. No appreciable change in weight occurred, the diets remained constant and all the patients continued to be satisfied. The insulin requirements remained the same,

except for a reduction of 5 units for 1 patient. There was some improvement in the general feeling of 2 patients. Riboflavin given in large amounts seems not to alter the degree of severity of diabetes. The patients afterward had no less severe diabetes than before the study began.

Thiamine-Riboflavin Therapy.—One of these patients was given a thiamine-insulin mixture to provide 3.3 mg. of thiamine and, in addition, 2 mg. of riboflavin daily by mouth. At the end of eight weeks no changes were found in weight, diet, insulin requirement or general feeling. Apparently with large doses of thiamine and riboflavin administered together to a well controlled diabetic patient no change occurs in the severity of the diabetic condition.

TABLE 4.—*Alfalfa Extract*

			Weight, Pounds		Diet, Gm.			Insulin, Units		Alfalfa		Symptoms Present		Symptoms Improved	
Patient	Age	Sex	Before	After	Carbohydrate	Protein	Fat	Beginning	End	Daily Dose, Ounces	Months Given	Specific	Nonspecific	Specific	Nonspecific
W. M.	29	M	148	147	135	90	120	50	50	3	4	0	+	0	0
J. M.	17	M	138	141	150	80	110	45*	45*	3	4	0	0	0	0
R. M.	16	F	112	130	150	80	80	70*	70*	3	4	0	0	0	0
Z. J.	55	M	142	138	160	80	100	42*	42*	3	4	0	+	0	+
M. G.	70	F	122	125	150	80	125	0	0	3	4	0	+	0	++
C. D.	64	M	118	122	200	80	135	20	20	3	4	0	+	0	++
W. S.	77	M	136	139	150	80	60	0	0	3	4	0	+	0	++
R. B.	57	M	113	115	170	80	120	40*	50*	3	4	0	+	0	0
J. S.	46	M	141	143	150	85	110	50*	50*	3	4	0	+	0	0
C. B.	19	F	148	148	180	100	70	45*	50*	3	4	0	0	0	0

* Protamine zinc insulin.

Alfalfa Extract Therapy.—A crude acid-alcoholic extract of powdered alfalfa leaves [3] was given to 10 of the well standardized patients for four months, again without definite influence on the diabetic state (table 4). Alfalfa leaves afford a rich source for all vitamin B fractions but contain little vitamin C. The crude extract is used satisfactorily and in large amounts in our outpatient clinic as a general tonic and for patients suspected of suffering from vitamin B inadequacy. As is commonly found with nondiabetic patients of older age groups, the diabetic patients given the alfalfa extract reported improvement in gen-

3. The extracting menstruum contained 0.4 per cent hydrochloric acid and 15 per cent ethyl alcohol. After two weeks' extraction of the powdered leaf, sodium hydroxide was added until the reaction remained only faintly acid to litmus, the heavy protein precipitate was filtered out and the alcohol content was brought up to 25 per cent by volume for preservation.

eral well-being,[4] but no change was found to occur in their diabetic state. So long as the dietary intake was kept constant, no alteration was found in their insulin requirements.

Thiamine and Riboflavin Content of Diabetic Diets.—In order to obtain an estimate of the patients' dietary intake of thiamine and riboflavin, close check was kept on the food actually consumed by each patient. Only the most reliable and cooperative patients were chosen for the study, so we feel that their statements as to food consumed are

TABLE 5.—*Thiamine and Riboflavin*

Patient	No.	Diet				Thiamine, Micrograms	Riboflavin, Micrograms	Total Nonfat Calories, Ratio
		Carbohydrate, Gm.	Protein, Gm.	Fat, Gm.	Calories			
B. A.	1	140	70	80	1,560	730	1,266	0.87
W. C.	2	170	70	100	1,860	1,050	2,154	1.09
F. N.	3	120	64	80	1,460	940	1,185	1.27
X. C.	4	175	75	110	1,990	765	1,175	0.76
I. J.	5	200	70	80	1,800	827	1,223	0.77
R. B.	6	175	80	110	2,010	982	1,171	0.96
I. S.	7	100	65	90	1,470	740	1,075	1.12
L. B.	8	170	85	110	2,010	1,091	1,307	1.06
C. B.	9	80	60	50	1,010	680	1,173	1.21
J. N.	10	150	85	140	2,200	874	1,405	0.93
J. M.	11	150	80	110	1,910	815	1,594	0.89
T. R.	12	110	60	40	1,040	769	731	1.13
J. S.	13	150	75	110	1,800	813	1,617	0.90
S. B.	14	120	70	80	1,480	469	1,715	0.62
G. A.	15	140	85	135	2,115	832	850	0.92
L. B.	16	180	60	120	2,040	940	1,167	0.98
R. H.	17	150	80	100	1,820	845	1,249	0.92
J. D.	18	210	120	150	2,670	1,175	2,004	1.05
N. R.	19	160	80	100	1,860	1,064	1,032	1.15
J. M.	20	120	70	120	1,840	791	1,446	1.04
Z. J.	21	160	80	140	2,220	964	1,681	1.00
R. C.	22	110	70	90	1,530	760	1,351	1.05
A. M.	23	200	80	135	2,335	977	1,553	2.87
W. R.	24	175	75	100	1,900	996	1,474	1.00
C. P.	25	165	70	140	2,200	878	1,213	1.02

as reliable as can be obtained from patients not under complete hospital supervision. The average daily intake of thiamine and riboflavin, as shown in table 5 for each patient, was calculated on the basis of the food content as given by Williams and Spies[5] for thiamine and by Fixsen and Roscoe[6] for all riboflavin except that derived from meats. For

4. The patients received 30 cc. of the extract three times a day, although the usual dose is only 30 cc. daily. The alcohol content of the extract may possibly have accounted for some of the increased sense of well-being.

5. Williams, R. R., and Spies, T. D.: Vitamin B_1 and Its Use in Medicine. New York, The Macmillan Company, 1939.

6. Fixsen, M. A., and Roscoe, M. H.: Tables of the Vitamin Content of Human and Animal Foods, Nutrition Abstr. & Rev. **7**:823-867, 1938.

meats we used the riboflavin values given by Mickelsen, Waisman and Elvehjem.[7]

If 600 Bourquin-Sherman units of riboflavin represent the normal person's daily need [8] and if 1 such unit is taken as equivalent to 3 micrograms, which are the values used in our calculation, it is seen (table 5) that most of our patients were receiving less than the normal 1.8 mg. of riboflavin daily. Their thiamine intake was also below the 1 mg. daily estimated by Williams and Spies as a crude minimal requirement. Requirement calculations are usually made on the basis of a 3,000 calory diet, however, while the diets of our patients ranged from 1,040 to 2,670 calories, with an average caloric value of only 1,805. If there does exist a quantitative relation between the rate of combustion and the vitamin requirement, then the dietary thiamine and riboflavin intake of our

TABLE 6.—*Normal Improvement in Diabetic State Under Continuous Control*

	Diet, Gm.			Insulin Requirement								
Patient	Carbohydrate	Protein	Fat	At Beginning	1 Week	2 Weeks	4 Weeks	6 Weeks	8 Weeks	10 Weeks	4 Months	1 Year
A. H.	120	80	70	35	30	25	20	10	0	0	0	0
L. B.	100	60	60	75	75	75	50	40	40	40	40	40
H. G.	140	80	125	27	25	25	20	18	15	10	0	0
N. B.	100	60	120	30	30	25	20	10	0	0	0	0
M. D.	100	70	100	54	50	50	40	30	25	15	0	0
J. S.	200	80	125	45	35	35	35	30	20	15	15	15
R. H.	225	66	100	60	50	35	30	30	30	30	30	..†
W. C.	170	70	100	75	50	50	50	40	30	20	20	20
W. I.	200	80	100	80	75	70	60	50	50	50	40	40
D. J.	100	60	50	32	30	25	15*	15	5	0	0	0

* Did not continue cooperation.
† Diet increased to 160 Gm. of carbohydrate, 75 Gm. of protein and 80 Gm. of fat.

patients was probably at a safe and adequate level. Our ratios of thiamine to nonfat calories in the diets average much above the normal value of 0.5 as given by Williams and Spies.

In the one paper (by Sindoni [9]) referred to by Williams and Spies as indicating a vitamin inadequacy in diabetic diets, there are found no quantitative data whatever as to the dietary intake of vitamins. Here again, uncontrolled diabetic patients who had previously been on

7. Mickelsen, O.; Waisman, H. A., and Elvehjem, C. A.: Recent Studies on the Vitamin Content of Meats and Meat Products, J. Am. Dietet. A. **15**:529-536, 1939.

8. Daniel, E. P., and Munsell, H. E.: Vitamin Content of Foods, Miscellaneous Publication 275, United States Department of Agriculture, 1937.

9. Sindoni, A., Jr.: Vitamin Deficiency in Prescription Diets of Diabetics: Study into Relationship of Diet Deficiency to Symptomatology as Observed in Eighty-Five Diabetics with Previous Dietary Treatment, Am. J. Digest. Dis. & Nutrition **3**:750, 1936.

unknown diets presumably inadequate in vitamin content showed symptomatic improvement and lessened insulin need after being placed under proper dietary and insulin control. This improvement Sindoni attributed to an increased intake of vitamins in the form of green vegetables and citrus fruits, but we point out the well known fact (table 6) that such improvement in the diabetic state regularly accompanies the placing of patients under proper dietary and insulin control alone.

COMMENT ON RESULTS

From the data here presented, there is found no evidence of benefit from thiamine or riboflavin therapy for well controlled diabetic patients except in the treatment of diabetic neuritis. Nor is there any obvious deficiency of these two vitamin factors in ordinary diabetic diets. Previously recommended vitamin therapy for diabetes would thus seem to be without basis in fact. Recommendations of such therapy have mainly been based on clinical testing of patients not adequately controlled before the tests were begun. In table 6 is shown the marked improvement diabetic patients exhibit in their ability to use dextrose, as their diabetic state is properly controlled through the months only by diet and insulin. They regularly show a reduction in insulin need as the months of adequate control pass. Eventually a basic level is reached for most adult diabetic patients—a level of insulin and dietary need at which they are maintained for long periods without change unless infection or other intercurrent disease disrupts their established balance.

In only 1 of our 25 patients who received the vitamin therapy was there any marked reduction in insulin need, and this patient was the only one not adequately standardized before the vitamin therapy was begun. Obviously our results have no bearing on the use of vitamin therapy in cases of uncontrolled diabetes or in conjunction with diet and insulin from the beginning of treatment. The urinary loss of large amounts of dextrose in cases of uncontrolled diabetes may perhaps lead to a vitamin depletion, but this has so far not been shown for any vitamin B fractions. Our results indicate only that in cases of well controlled diabetes there appears to be no need for thiamine or riboflavin beyond the amounts present in ordinary diabetic diets, except in the case of diabetic neuritis. On this condition thiamine seems to exert almost a specific effect. The fact that in most cases of such neuritis improvement also occurs when the diabetic state is brought under proper control by diet and insulin might suggest a thiamine deficiency during the uncontrolled period, but there also exists the possibility that the improvement in neuritis results only from increased tissue combustion of sugar under insulin therapy and not from a specific lack of thiamine.

Our negative results with thiamine and riboflavin therapy may be criticized by some investigators on account of the relatively small amounts given. Such criticism would be justified if we had admin-

istered the vitamins only for short periods. But when the vitamins are given for several months in amounts two or three times the normal minimal daily requirement and in addition to an adequate dietary supply, there would seem to be little doubt that any vitamin deficit in the body tissues will have been covered.

The possibilities of vitamin C inadequacy in cases of uncontrolled diabetes or of therapeutic use of the vitamin in conjunction with the usual dietetic and insulin management of the disease are at present under investigation.

Actual and severe vitamin deficiency may play a part in one important complication—diabetic coma. In this condition food and vitamin intake ceases, usually in the presence of a fever which causes heightened combustion. Nor do the usual methods of treatment of coma provide for any replenishment of vitamins. The most severe evidences of damage due to coma occur in those tissues with the highest rate of combustion and hence with the greatest need for the vitamin B fractions—the brain, the kidney and the heart muscle. We are at present investigating this phase of diabetic coma with a view to adding intensive vitamin therapy to our usual treatment of such coma. Certainly diabetic coma still presents an unsolved clinical problem, with a fatality rate as high as in the early days of insulin therapy.

CONCLUSIONS

1. Usual diabetic diets, as routinely used for our patients, contain adequate amounts of thiamine and riboflavin in relation to their total caloric value.

2. Administration of large amounts of thiamine and riboflavin to well controlled diabetic patients over many weeks does not reduce the insulin requirement or alter the severity of the diabetic state.

3. In cases of well controlled diabetes there seems no need for thiamine or riboflavin beyond the amounts provided by ordinary diabetic diets. This holds true except for patients suffering from diabetic neuritis, a condition in which thiamine therapy seems to result in prompt improvement or cessation of the neuritic symptoms.

4. Dextrose tolerance regularly increases in diabetic patients as their diabetic state is controlled by diet and insulin through the first few months. Many of the claims of benefit from vitamin therapy have been based on clinical testing carried out on patients before they had been brought under proper control by diet and insulin or before they had reached a stable state.

Dr. C. A. Mills gave constructive suggestions and criticism during the study and in the preparation of the manuscript.

The thiamine was supplied by Eli Lilly & Co., and the riboflavin by Merck & Co., Inc.

PANCREATIC SECRETION IN MAN AFTER STIMULATION WITH SECRETIN AND ACETYLBETA-METHYLCHOLINE CHLORIDE

A COMPARATIVE STUDY

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Secretory activity of the pancreas may be stimulated by either a humoral (secretin) or a neural (vagal) mechanism. The amount and type of secretion produced by the two mechanisms has been shown to differ widely in animals. Stimulation with secretin produces a large volume of pancreatic juice rich in bicarbonate and poor in enzymes, whereas vagal stimulation produces a scant flow of juice poor in bicarbonate and rich in enzymes. Mellanby [1] hypothesized that the content of enzymes in the pancreatic juice is determined by action of the vagus nerves, whereas the concentration of the bicarbonate solution in which these enzymes are contained is determined by the action of secretin. In a clinical study of pancreatic function, the response of the pancreas to both types of stimulants should be determined in order to obtain a complete picture.

In man, the effect of intravenous injection of purified secretin was first studied, in 1926, by Chiray, Salmon and Mercier.[2] They reported an increase in the amount of juice obtained by means of an Einhorn duodenal tube, as well as an increase in the concentration of trypsin and lipase. Voegtlin, Greengard and Ivy,[3] in 1934, reported an extensive investigation of the effects in man of intravenous injections of secretin prepared by Ivy. They showed that the volume of secretion and the total output of enzymes increased during the first fifteen minutes after

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1. Mellanby, J.: The Mechanism of Pancreatic Digestion—The Function of Secretin, J. Physiol. **60**:85-91 (May) 1925.

2. Chiray, M.; Salmon, A. R., and Mercier, A.: Action de la sécrétine purifiée sur la sécrétion externe du pancréas de l'homme, Bull. et mém. Soc. méd. d. hôp. de Paris **50**:1417-1426 (July 30) 1926.

3. Voegtlin, W. L.; Greengard, H., and Ivy, A. C.: The Response of the Canine and Human Pancreas to Secretin, Am. J. Physiol. **110**:198-224 (Nov.) 1934.

injection but that the concentration of enzymes did not decrease or increase consistently. In 1936, Chiray and Bolgert [4] published the results of an extensive investigation in which it was shown that the volume of pancreatic juice and the total quantity of enzymes increased after administration of secretin intravenously. A year later, Ågren and Lagerlöf [5] reported their results with secretin prepared by Hammersten and Ågren; they found that when injected intravenously secretin produced a rapid increase in the volume of secretion and a rise in the concentration of bicarbonate therein contained, whereas the concentration of the enzymes amylase and trypsin fell. This indicated a washing out of the preformed enzymes stored in the pancreatic system, followed by secretion of the recently formed enzymes, for the most part sustained at a lower level of concentration. A large quantity of enzyme was excreted during the first ten minutes.

Ågren and Lagerlöf devised a double tube; one lumen was used to keep the stomach free of secretion and the other to aspirate the duodenal contents. By this means they prevented the entrance of gastric contents into the duodenum, avoided the admixture of gastric and duodenal contents and thus obtained much greater accuracy in the analysis of the duodenal contents than had previously been possible. In the United States, Diamond, Siegel, Gall and Karlen,[6] using the same method and the same secretion, have confirmed recently the results of Ågren and Lagerlöf.

Although the drugs which act as stimulants of the parasympathetic nervous system have been used frequently to study the effect of vagal stimulation on pancreatic secretion in animals, references to their use for this purpose in man are not numerous. Pilocarpine is reported [7] as having both increased and decreased [8] the rate of secretion; physostigmine increases the rate, as does mecholyl chloride. These

4. Chiray, M., and Bolgert, M.: Mesures de la sécrétion pancréatique externe en clinique par l'épreuve à la sécrétine purifiée, Nutrition **6**:223-230, 1936.

5. Ågren, G., and Lagerlöf, H.: The Pancreatic Secretion in Man After Intravenous Administration of Secretin, Acta med. Scandinav. **90**:1-29, 1936.

6. Diamond, J. S.; Siegel, S. A.; Gall, M. B., and Karlen, S.: The Use of Secretin as a Clinical Test of Pancreatic Function, Am. J. Digest. Dis. **6**:366-372 (Aug.) 1939.

7. Holsti, O.: Beiträge zur Kenntnis der Pankreassekretion beim Menschen, Deutsches Arch. f. klin. Med. **111**:48-92 (June) 1913. Snyder, W. H., Jr., and Lium, R.: Pancreatic Fistula: A Case with Intubation of Wirsung's Duct, Surg., Gynec. & Obst. **62**:57-64 (Jan.) 1936. Villaret, M., and Justin-Besançon, L.: Étude clinique et physiologique d'une fistule pancréatique, Arch. d. mal. de l'app. digestif **15**:751-767 (Oct.) 1925.

8. McCaughan, J. M.; Sinner, B. L., and Sullivan, C. J.: The External Secretory Function of the Human Pancreas: Physiologic Observations, Arch. Int. Med. **61**:739-754 (May) 1938.

reports pertain to the effects of the drugs on patients who had external pancreatic fistulas. Loeper, Lemaire and Dany [9] used acetylcholine as a stimulant of pancreatic function in a few cases; they obtained the duodenal contents by the use of a duodenal tube. Detailed data on the effect of drugs that stimulate the parasympathetic nervous system on external pancreatic secretion are apparently not available.

The purpose of this investigation was (1) to obtain further data on the action of secretin in man, particularly in regard to p_H values and to lipase; (2) to study the effect of parasympathetic stimulants on external pancreatic secretion in man; (3) to compare the amount and quality of secretion produced after vagal stimulation with that produced after stimulation with secretin, and (4) to develop a method by means of which pancreatic secretion produced by vagal stimulation might be studied clinically.

EXPERIMENTAL METHOD

After the subject had experienced a twelve hour fast, a double tube, devised by Ågren and Lagerlöf, was introduced into the duodenum; it was allowed to descend until bile was recovered from both the gastric and the duodenal lumens. The tube then was withdrawn slowly until gastric juice was flowing from the gastric lumen of the tube and duodenal contents from the duodenal lumen of the tube. The position of the tube was determined by roentgen examination.

Continuous aspiration with a negative pressure of 16 to 25 inches (40.5 to 63.5 cm.) of water was carried out. This negative pressure was found to be sufficient for the prevention, to a great extent, of the overflow of gastric juice into the duodenum and for the collection of duodenal contents.

The duodenal contents were studied in four ten minute periods before stimulation and into four ten minute periods and two twenty minute periods after stimulation. The effect of various positions on aspiration was studied; a position was finally adopted in which the patient was half reclining on his back.

A purified secretin was used; 1 clinical unit for each kilogram of body weight was injected intravenously. Acetylbetamethylcholine chloride (mecholyl chloride) was chosen from among the parasympathetic stimulants. After numerous trials, it was found that 15 mg. given subcutaneously usually produced a measurable effect on pancreatic secretion; doses greater than 15 mg. tended to stimulate gastric secretion so greatly that entrance of the gastric contents into the duodenum was difficult to prevent.

Fourteen normal subjects were used. Twenty experiments with secretin as a stimulant were carried out on 13 of the 14 subjects, and 22 experiments with mecholyl chloride were carried out on 10 of the 14 subjects. A single test with secretin as a stimulant was carried out on 7 subjects, two tests on 5 subjects and three tests on 1 subject. With mecholyl chloride as a stimulant a single test was carried out on each of 5 subjects; two tests on each of 2 subjects; three tests on 1 subject; five tests on 1 subject, and seven tests on 1 subject.

Cloudiness of the duodenal contents indicated admixture of gastric contents. All clouded fractions were discarded. Entrance of the gastric contents into the

9. Loeper, M.; Lemaire, A., and Dany, H.: Influence de l'atropinisation sur la résponse vésiculaire à l'acétylcholine, Compt. rend. Soc. de biol. **113**:1478-1479, 1933.

duodenum occurred infrequently but occurred more often when mecholyl chloride was used as a stimulant than when secretin was so used. Spilling over of the acid gastric contents occurred most frequently with subjects who had hyperacidity.

CHEMICAL METHODS

Hydrogen ion concentration (p_H) was determined by the quinhydrone-electrode method. Amylase activity was determined by the method of Norby[10] as modified by Ågren and Lagerlöf. Determinations of the activity of trypsin were carried out by the procedure given by Ågren and Lagerlöf, which is the method outlined by Willstätter, Waldschmidt-Leitz, Dūnaiturria, and Künstner[11] and modified by Christiansen.[12] The activity of lipase was determined by the method of Crandall and Cherry,[13] as reported by us in previous studies, with a 1:10 dilution of specimens from the duodenum.[14]

EXPERIMENTAL DATA

If more than one test was carried out on a single subject, the average result of all the tests done on that person is given in tables 1, 2, 3, 4 and 5. The data presented in the tables are based on too few experiments to give precise means and extremes. However, analysis of individual cases will show that the averages depict the behavior of the various factors studied. Averages have been used in construction of the curve represented in charts 1 to 8.

Volumes of content recovered in control tests on the same person showed remarkable agreement, considering the technical difficulties involved in removing the duodenal contents quantitatively. Thus, in the first ten minute period after stimulation with secretin, the volumes were 18 and 24 cc. in 1 case; 34, 32 and 62 cc. in a second case; 48 and 53 cc. in a third case, and 25 and 20 cc. in a fourth case. The volumes in the first forty minute period following stimulation with secretin in the same cases were, respectively, 93 and 93 cc.; 156, 233 and 203 cc.; 111 and 128 cc., and 135 and 95 cc. A somewhat greater variation in the volumes was obtained after stimulation with mecholyl chloride. The p_H values as well as the values for several enzymes were likewise comparatively constant for the same subject after stimulation.

Effect of Stimulation on the Gross Appearance of Duodenal Contents.—After the injection of secretin the volume of duodenal contents recovered increased markedly. The effect of this was noticeable within a short period, usually a minute; the normal biliary color of the duodenal contents rapidly became less marked,

10. Nørby, cited by Ågren and Langerlöf.[5]

11. Willstätter, R.; Waldschmidt-Leitz, E.; Dūnaiturria, S., and Künstner, G.: Zur Kenntnis des Trypsin: XV. Abhandlung über Pankreasenzyme, Ztschr. f. physiol. Chem. **161**:191-210, 1926.

12. Christiansen, T.: Kliniske Studier over den digestive Duodenalsaftsekretion: Samt et Bidrag til Sporgsmaalit om den exokrine Pancreasfunktion ved Achylia gastrica, Copenhagen, Levin & Munksgaard, 1933.

13. Crandall, L. A., Jr., and Cherry, I. S.: Presence of an Olive Oil Splitting Lipase in the Blood of Patients with Multiple Sclerosis, Proc. Soc. Exper. Biol. & Med. **28**:572-574 (March) 1931.

14. Comfort, M. W.; Parker, R. L., and Osterberg, A. E.: The Concentration of Pancreatic Enzymes in the Duodenum of Normal Persons and Persons with Disease of the Upper Part of the Abdomen, Am. J. Digest. Dis. **6**:249-254 (June) 1939.

and in many instances a clear, almost colorless secretion was obtained. The yellowish color reappeared, however, after a short time.

After administration of mecholyl chloride there was a slight increase in volume, and in many instances dark bile appeared soon after injection of the drugs, indicative of emptying of the gallbladder.

Volume of Duodenal Contents.—Before stimulation the volume of duodenal contents varied from 1 to 20 cc., the average being 8.78 cc. for a ten minute period (table 1). After stimulation with secretin the volume increased markedly in every instance, being greater in the first ten minute period after stimulation than during any ten minute period before stimulation (more than 20 cc., with an average of 39 cc.). The greatest volume was recovered in 9 cases in the first, in 3 cases in the second and in 1 case in the third ten minute period. The increase in the first ten minute period ranged from one-half to tenfold, averaging fourfold.

TABLE 1.—*Volume of Duodenal Contents Before and After Stimulation with Secretin and Mecholyl Chloride*

	Before Secretin, 10 Minute Periods		After Secretin						Before Mecholyl Chloride		After Mecholyl Chloride					
			10 Minute Periods				20 Minute Periods		10 Minute Periods		10 Minute Periods				20 Minute Periods	
Case	2	1	1	2	3	4	5	6	2	1	1	2	3	4	5	6
1	20	—	32	18	—	—	20	14	..	..	..	..	..	..	..	..
2	12	14	21	21	34	24	30	20	9	11	20	32	20	5	15	13
3	8	13	43	49	53	43	60	34	14	19	26	24	38	14	19	18
4	..	..	..	..	..	..	..	..	8	7	7	6	21	11	9	65
5	3	8	63	18	15	25	50	16	..	..	..	..	..	..	..	..
6	10	18	50	19	15	34	31	12	10	4	14	10	5	4	11	8
7	3	1	22	29	28	35	40	32	2	7	7	10	4	1	0.5	3
8	6	—	46	34	25	27	29	10	7	7	18	8	—	7	11	—
9	10	13	31	24	47	21	9	5	..	..	..	..	..	..	..	..
10	7	11	32	29	29	25	26	39	..	..	..	..	..	..	..	..
11	—	—	44	23	21	24	6	—	—	8	18	3	5	13	6	5
12	—	—	32	30	20	18	44	—	—	2	—	—	8	5	17	—
13	4	6	37	22	19	12	27	19	5	4	14	—	2	—	6	4
14	11	7	52	23	28	17	38	—	7	7	13	11	14	10	3	2
Average	7.0	10.2	39.0	26.1	27.9	25.5	31.6	....	7.9	7.8	14.5	13.2	13.1	7.8	9.8	40.8
Range..	3.0- 20.0	1.5- 18.0	21- 52	18- 48.7	15- 53	12- 43	6- 59.7	5- 33.7	2.5- 13.8	2.5- 18.8	7- 26	3- 31.6	2- 38.3	1- 13.9	0.5- 18.8	2- 65

After the maximal degree of increase there was usually a slight fall, but the volume usually was maintained at a level much greater than that which existed before stimulation. The volume declined thereafter, reaching prestimulation levels in sixty to eighty minutes.

After stimulation with mecholyl chloride, the volume of secretion rose in 8 subjects but was maintained at its prestimulation levels in 2 (table 1). The greatest rise occurred in 4 cases in the first, in 2 cases in the second and in 4 cases in the third ten minute period. At some time during the forty minute period after stimulation, the volume increased from one to threefold. The small increase in volume after administration of mecholyl chloride is in contrast with the great increase that occurred after secretin was given (chart 1).

Hydrogen Ion Concentration of Duodenal Contents.—Before stimulation, the hydrogen ion concentration varied between 6.35 and 7.78; the average was 7.05 (table 2). After stimulation with secretin, a definite increase in hydrogen ion concentration occurred in every case. In all cases a rise of at least 1 p_H unit occurred; in 12 of the 13 subjects a p_H of at least 8 was reached after stimulation

with secretin. On the other hand, after stimulation with mecholyl chloride there was no significant change in the hydrogen ion concentration. In chart 2 the contrasting tendencies after stimulation with secretin and mecholyl chloride are illustrated.

Concentration of Amylase in Duodenal Contents.—Before stimulation, the concentration of amylase in terms of grams of maltose liberated per cubic centimeter of duodenal contents varied from 1.03 to 3.10 Gm., averaging 1.3 Gm. (table 3). After stimulation with secretin, the concentration of amylase rose in 6 subjects, fell in 5 subjects and remained unchanged in 2 subjects in the first ten minute period. The response was entirely different in the second ten minute period, during which a fall in concentration occurred in all 13 cases (100 per cent), reaching a level below that found before stimulation in each person studied. The concentration decreased to less than 0.6 Gm. in every case and to less than 0.5 Gm. of maltose per cubic centimeter of duodenal contents in 10 of the 13 cases. The

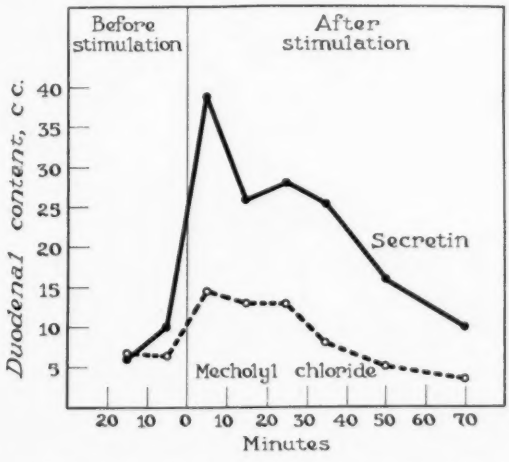

Chart 1.—Average volume of duodenal contents per unit of time before and after stimulation with secretin and mecholyl chloride.

concentration remained below prestimulation levels in 8 of 10 cases during the third and fourth ten minute periods. The lowest concentration was found in 12 of the 3 cases in the second ten minute period and in 2 of the 13 in the third. Although the concentration tended to remain below the prestimulation levels, a rise occurred above that of the second ten minute period in 8 of 10 cases in the third ten minute period and above that of the third period in 8 of 10 cases in the fourth ten minute period. The concentration did not return to prestimulation levels during the eighty minutes in 9 cases but did return to the prestimulation levels once in the thirty to forty minute period and twice in the forty to sixty minute period. In other words, secretin produces a prolonged depression of the concentration lasting forty to eighty minutes or longer, which is greatest in the second ten minute period and is followed by a slight secondary rise which may or may not reach prestimulation levels in eighty minutes.

The effect of stimulation with mecholyl chloride is strikingly different from that of stimulation with secretin (table 3). After stimulation with mecholyl chloride the concentration increased in every case during the first ten minute period; the maximal concentration was obtained in 2 cases in the first, in 2 cases in the second, in 2 cases in the third and in 3 cases in the fourth ten minute period and in 1 case in the forty to sixty minute period. In 9 of the 10 cases a concentration of more than 3.7 Gm. of maltose per cubic centimeter of duodenal contents was reached, whereas a concentration of more than 4 Gm. of maltose per cubic centimeter of duodenal contents was reached in 8 of the 10 cases and more than 5 Gm. of maltose in 4 of 10 cases. A concentration greater than prestimulation levels was maintained for forty minutes in all 10 cases, for sixty minutes in 8 of 10 cases and for eighty minutes in 7 of 9 cases. In short, a prolonged rise in concentration occurs after stimulation with mecholyl chloride that persists for sixty to

TABLE 2.—*P_H Values of Duodenal Contents Before and After Stimulation with Secretin and Mecholyl Chloride*

	Before Secretin, 10 Minute Periods		After Secretin						Before Mecholyl Chloride 10 Minute Periods		After Mecholyl Chloride					
			10 Minute Periods				20 Minute Periods				10 Minute Periods				20 Minute Periods	
Case	2	1	1	2	3	4	5	6	2	1	1	2	3	4	5	6
1	6.5	—	7.6	8.6	—	—	8.2	8.2	..	..	..	..	..	..	..	..
2	6.7	7.2	7.8	8.3	7.7	7.5	7.6	7.5	7.4	7.3	7.1	7.1	7.0	7.9	7.2	7.3
3	7.0	7.1	7.8	8.1	7.9	7.9	7.9	8.0	7.4	7.2	7.3	7.2	7.4	7.4	7.5	7.5
4	..	..	..	..	..	..	..	..	7.7	7.8	7.8	7.8	7.7	7.9	7.7	7.7
5	—	7.4	7.7	7.7	8.2	7.9	7.3	7.8	..	..	..	..	..	..	..	..
6	7.4	6.9	7.8	8.3	8.3	7.9	7.7	7.9	6.7	7.0	7.2	7.2	7.1	7.3	6.6	6.0
7	6.5	6.7	7.6	8.0	8.0	7.1	7.0	7.0	7.1	6.6	7.1	7.1	7.3	7.1	7.0	6.8
8	6.4	—	7.4	8.1	7.9	8.0	7.7	7.9	7.2	6.9	7.3	7.2	—	6.6	6.5	—
9	6.5	6.4	7.4	7.5	7.1	7.3	7.2	7.2	..	..	..	..	..	..	..	..
10	7.0	7.0	7.7	8.2	8.1	8.1	8.0	7.9	..	..	..	..	..	..	..	..
11	—	6.5	7.7	7.9	8.1	7.4	7.7	—	—	7.3	7.4	7.1	7.1	8.2	7.1	8.2
12	—	—	7.2	7.9	7.9	7.9	7.4	—	—	6.7	—	—	6.9	7.8	6.4	—
13	6.9	7.1	7.9	8.2	8.2	8.2	7.9	7.5	7.6	7.5	7.3	7.2	—	7.0	—	7.7
14	7.3	7.4	7.9	8.1	8.2	8.2	8.1	—	7.6	7.7	7.2	7.4	7.4	7.3	7.7	7.8
Average	6.83	6.96	7.65	8.08	7.98	7.80	7.67	7.68	7.34	7.21	7.30	7.27	7.24	7.47	7.07	7.38
Range..	6.4- 7.4	6.4- 7.4	7.2- 7.9	7.5- 8.6	7.1- 8.3	7.1- 8.1	7.0- 8.2	6.9- 8.2	6.7- 7.7	6.6- 7.7	7.1- 7.8	7.1- 7.8	6.9- 7.4	6.6- 7.9	6.4- 7.7	6.8- 8.2

eighty minutes or longer. The contrasting responses to the two types of stimulants are represented in chart 3.

Amylase Value per Total Sample.—Before stimulation, the total value for amylase in terms of grams of maltose liberated by all the duodenal contents recovered per ten minute period varied from 1.12 to 54.07 Gm., an average of 10.8 Gm. (table 3). After stimulation with secretin, a rapid increase in the total amylase in terms of grams of maltose liberated from the first ten minute fraction of duodenal contents occurred in 12 of 13 cases. The increase varied from a fraction to fourteenfold and averaged fourfold. In 12 of the 13 cases the total amylase varied from 10 to 70 Gm. of maltose; the maximal value per ten minute period occurred in the first period in 12 of the 13 cases. The rapid increase in the total amylase in the first ten minute period was followed by a rapid fall in the second ten minute period in all cases; in 7 of 11 cases it decreased to levels less than those obtained before stimulation. The fall usually was followed by a slight rise in the third and fourth ten minute periods which persisted during the first twenty minute period, but it is to be noted that the total value was only slightly greater than prestimulation levels in the third and fourth ten minute period and the first twenty

minute period. Although there is a diminution in concentration after stimulation with secretin, the total value for amylase is increased. It is significant that the total value for amylase per ten minute period was increased in 12 of 13 cases only during that ten minute period following stimulation, when the concentration was not decreased and the volume was largest after stimulation. As soon as the concentration fell (second ten minute period), the total value fell in spite of the persistent secretion of large volumes. The large total value for amylase in the first ten minute period has resulted from the washing out of the enzyme in the cells, not from stimulation of the cell.

After stimulation with mecholyl chloride an increase in total amylase occurred in all 10 cases (table 3). The increase varied from twofold to tenfold and averaged fourfold. In 5 of 9 cases the total value was 70 Gm. of maltose per ten minute fraction of duodenal contents, a value greater than that usually attained after stimulation with secretin. Although the rise was well sustained, the maximal

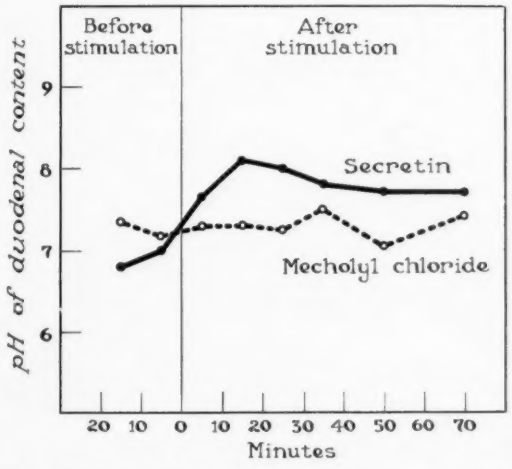

Chart 2.—Average p_H of samples of duodenal contents per unit of time before and after stimulation with secretin and mecholyl chloride.

value occurred in 4 cases in the first period, in 2 cases in the second, in 2 cases in the third and in 2 cases in the fourth period, the total value per unit period returning to prestimulation levels in 1 instance in twenty to thirty minutes, in 2 instances in thirty to forty minutes, in 1 instance in forty to sixty minutes and in 3 instances in sixty to eighty minutes but persisting beyond eighty minutes in the remaining 4 cases. Mecholyl usually produces a prolonged, sustained rise in the total value for amylase, contrasting with the sharp rise and rapid fall characteristic of the influence of secretin on the total amylase per unit period (chart 4).

Concentration of Trypsin.—Before stimulation, the concentration of trypsin, in terms of cubic centimeters of tenth-normal potassium hydroxide per cubic centimeter of duodenal contents, varied from 0.6 to 3.2 cc., averaging 1.60 cc. (table 4). After stimulation with secretin the concentration fell in 8 cases and rose in 4 cases in the first ten minute period. A fall occurred in 13 cases (100 per cent) in the second

TABLE 3.—*Concentration of Amylase Before and After Stimulation with Secretin and Mecholyl Chloride (Grams Maltose per Cubic Centimeter of Duodenal Contents)*

Case	Before Secretin, 10 Minute Periods		After Secretin: 10 Minute Periods				After Secretin: 20 Minute Periods		Before Mecholyl Chloride, 10 Minute Periods		After Mecholyl Chloride: 10 Minute Periods				After Mecholyl Chloride: 20 Minute Periods	
	2	1	1	2	3	4	5	6	2	1	1	2	3	4	5	6
1	1.03	—	1.72	0.26	—	—	1.38	1.38	....	....	....	....	....	....	....	....
2	1.12	1.20	0.69	0.39	0.86	0.52	1.55	0.86	1.44	1.17	2.75	3.47	3.44	4.82	4.13	2.28
3	1.63	1.69	1.58	0.55	0.86	0.77	1.09	1.52	2.21	3.10	4.13	5.43	4.82	3.75	2.92	2.32
4	....	....	....	....	....	....	....	....	0.52	1.72	2.06	3.44	4.47	2.75	3.78	3.44
5	1.72	1.38	1.03	0.26	0.34	0.09	1.03	0.69	....	....	....	....	....	....	....	....
6	0.47	0.52	0.43	0.15	0.21	0.47	0.30	0.34	0.86	0.86	1.03	1.46	2.67	2.75	3.78	0.52
7	1.03	0.69	0.69	0.34	0.28	0.56	0.52	0.52	1.63	1.51	4.47	3.10	3.78	3.01	2.92	2.24
8	1.55	—	0.77	0.43	0.69	0.43	0.09	0.95	1.38	1.03	3.10	2.84	—	4.82	3.10	—
9	0.69	1.03	1.03	0.26	0.30	0.52	0.43	0.30	....	....	....	....	....	....	....	....
10	0.77	0.52	0.69	0.04	0.13	0.09	0.19	0.26	....	....	....	....	....	....	....	....
11	—	—	1.46	0.60	0.95	1.03	1.55	—	—	0.86	1.72	1.55	5.50	5.85	5.85	5.16
12	—	—	0.69	0.26	0.17	0.09	0.86	—	—	1.03	—	—	1.03	1.72	1.03	—
13	0.34	0.34	0.77	0.09	0.34	0.52	1.12	1.20	1.72	2.24	6.19	5.68	—	3.78	—	2.41
14	1.38	1.20	1.89	0.52	0.52	0.52	0.86	—	2.58	1.89	4.18	5.68	4.47	4.64	4.13	3.44
Average.....	1.067	0.952	1.034	0.318	0.471	0.566	0.889	0.801	1.543	1.540	3.293	3.627	3.774	3.790	3.517	2.725
Range.....	1.03-1.72	0.34-1.69	0.43-1.89	0.04-0.60	0.13-0.95	0.09-1.03	0.19-1.55	0.26-1.52	0.52-2.58	0.86-3.10	1.03-6.19	1.46-5.68	1.03-5.51	1.72-5.85	1.03-5.85	0.52-5.16

Total Values of Amylase Before and After Stimulation with Secretin and Mecholyl Chloride (Grams Maltose per Total Sample)

1	20.64	—	55.04	4.64	—	—	27.52	19.26	....	....	....	....	....	....	....	....
2	13.42	16.86	14.44	7.87	20.64	12.38	47.82	22.05	13.07	14.79	56.15	106.38	75.70	24.09	58.83	36.46
3	13.07	22.42	59.81	26.40	45.58	33.28	61.61	55.70	26.78	54.07	108.13	125.80	112.45	51.26	37.79	45.41
4	.....	.....	.....	.....	.....	.....	.....	.....	4.13	12.04	14.45	22.37	93.95	30.27	34.06	22.36
5	5.16	11.01	65.02	4.64	5.16	17.20	51.60	11.01	....	....	....	....	....	....	....	....
6	5.08	9.29	21.50	2.84	2.79	16.51	9.93	5.24	8.69	4.13	19.95	17.98	12.55	11.87	41.62	4.13
7	3.10	1.12	15.77	10.15	7.74	19.91	20.64	16.51	3.61	7.22	33.56	31.99	18.65	3.01	1.46	6.71
8	9.29	—	35.13	15.48	16.68	11.78	17.89	9.20	9.64	7.91	57.28	22.02	—	33.73	34.06	—
9	6.88	13.42	31.99	6.19	14.15	10.84	3.87	1.50	....	....	....	....	....	....	....	....
10	5.42	5.68	22.02	1.25	3.74	2.15	5.02	10.06	....	....	....	....	....	....	....	....
11	—	—	64.76	13.84	12.06	14.25	9.29	—	—	6.88	30.96	4.64	27.53	76.05	35.10	25.81
12	—	—	22.36	7.74	3.44	12.38	37.84	—	—	2.58	—	—	8.26	8.60	17.54	—
13	1.38	2.34	27.53	1.89	6.54	6.19	30.19	22.88	9.46	8.95	85.69	45.41	—	11.35	—	9.03
14	15.14	8.43	98.38	11.87	14.45	8.77	32.68	—	18.07	13.24	53.66	62.44	62.64	46.44	12.38	6.88
Average.....	8.96	10.06	41.06	8.83	12.75	13.80	27.61	17.34	11.67	13.18	51.09	48.78	51.47	29.67	30.32	19.67
Range.....	1.38-20.64	1.12-22.42	14.44-98.38	1.25-26.40	2.79-45.58	2.15-33.28	3.87-61.61	1.50-55.70	4.13-26.78	2.58-54.07	14.45-108.13	4.64-106.38	8.26-112.45	3.01-76.05	1.46-58.83	4.13-36.46

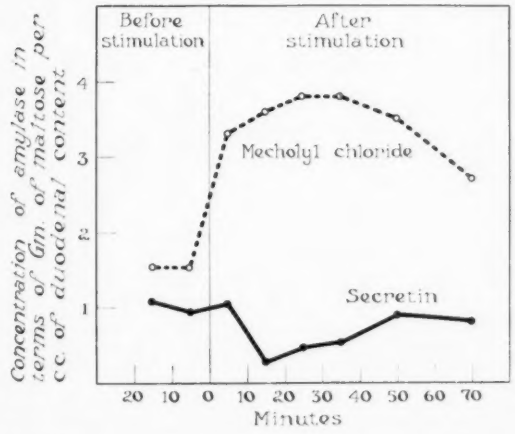

Chart 3.—Average concentration of amylase per cubic centimeter of duodenal contents in a sample obtained per unit of time before and after stimulation with secretin and mecholyl chloride.

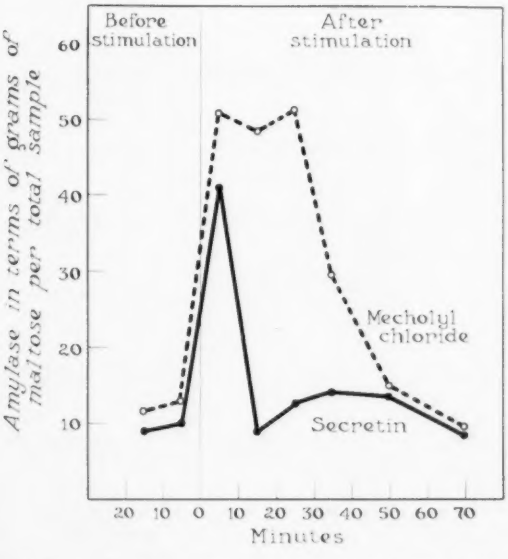

Chart 4.—Average value for total amylase per total sample obtained per unit of time before and after stimulation with secretin and mecholyl chloride.

TABLE 4.—*Concentration of Trypsin in Duodenal Content Before and After Stimulation with Secretin and Mecholyl Chloride (Cubic Centimeters of Tenth-Normal Potassium Hydroxide per Cubic Centimeter of Duodenal Juice)*

	Before Secretin, 10 Minute Periods		After Secretin						Before Mecholyl Chloride, 10 Minute Periods		After Mecholyl Chloride					
			10 Minute Periods				20 Minute Periods				10 Minute Periods				20 Minute Periods	
Case	2	1	1	2	3	4	5	6	2	1	1	2	3	4	5	6
1	1.5	—	1.8	0.2	—	—	0.9	0.7	...	...	...	...	...	...	...	...
2	1.3	1.2	0.6	0.5	—	0.8	1.1	1.3	2.0	2.3	2.5	2.6	2.3	3.2	2.6	2.0
3	2.1	2.0	1.0	0.7	0.9	1.4	1.0	1.3	2.0	2.3	3.1	3.1	2.1	1.8	1.5	2.0
4	...	...	...	...	...	...	...	...	1.6	2.0	1.8	2.6	3.2	0.6	2.8	3.0
5	2.0	1.0	0.9	0.3	0.7	1.1	1.6	1.0	...	...	...	...	...	...	...	...
6	1.0	1.1	1.0	0.7	0.7	1.1	1.1	0.8	3.0	2.3	2.9	3.0	3.2	3.1	3.0	2.0
7	2.6	3.2	1.0	0.6	0.8	1.0	1.3	1.4	1.4	1.2	2.9	2.1	1.7	1.6	...	1.4
8	...	...	1.0	0.9	0.4	0.75	0.8	0.8	1.7	1.8	2.3	2.1	—	2.5	2.3	—
9	0.6	1.4	1.3	0.6	0.3	1.0	0.8	0.8	...	...	...	...	...	...	...	...
10	1.7	1.2	3.7	0.6	0.5	0.4	0.4	0.2	...	...	...	...	...	...	...	...
11	—	0.9	1.5	0.7	1.0	1.1	1.5	—	—	0.7	1.7	3.3	2.5	—	2.6	2.7
12	...	...	1.1	0.9	0.9	1.1	1.3	—	—	1.5	—	—	1.3	1.6	1.2	—
13	1.4	1.8	1.6	0.2	0.8	0.8	1.1	1.5	1.0	1.5	2.5	2.5	—	2.5	—	1.4
14	1.2	1.0	1.2	0.9	0.8	0.9	1.1	—	1.7	1.3	1.9	2.5	2.1	2.3	2.5	—
Average.....	1.54	1.48	1.37	0.60	0.72	0.96	1.08	0.98	1.81	1.69	2.41	2.65	2.31	2.14	2.14	2.07
Range.....	0.6-2.6	1.0-3.2	0.6-1.8	0.2-0.9	0.3-1.0	0.7-1.4	0.4-1.6	0.2-1.5	1.0-3.0	0.7-2.3	1.7-3.5	2.1-3.3	1.3-3.2	0.6-3.2	0.7-3.0	1.4-3.0

Total Trypsin of Duodenal Contents Before and After Stimulation with Secretin and Mecholyl Chloride (Cubic Centimeters of Tenth-Normal Potassium Hydroxide per Total Sample)

1	30.0	—	57.6	3.6	—	—	18.0	9.8	...	...	...	...	...	...	...	...
2	15.6	16.8	23.5	11.2	—	9.2	34.2	22.4	15.6	24.7	27.1	80.9	53.3	16.0	40.4	28.2
3	16.8	24.6	43.1	33.8	47.7	60.0	61.1	59.9	27.3	43.5	79.5	68.6	69.8	23.9	25.6	39.4
4	....	....	....	....	....	....	....	....	12.8	14.0	12.6	16.9	67.2	6.6	25.2	19.5
5	6.0	8.0	56.7	5.4	10.5	27.5	80.0	16.0	...	...	...	...	...	...	...	...
6	10.6	20.7	50.8	13.8	11.7	37.5	36.8	11.4	30.0	8.3	41.6	29.8	16.8	14.3	33.0	16.0
7	7.8	6.4	24.0	15.5	21.8	35.6	52.0	44.8	3.7	7.8	24.0	22.1	8.9	1.6	1.4	4.2
8	—	—	45.1	30.0	11.1	20.6	24.4	11.0	11.9	14.4	44.1	17.2	—	17.5	25.3	...
9	6.0	18.2	40.3	14.4	14.1	21.0	7.2	4.0	...	...	...	...	...	...	...	...
10	11.9	13.2	118.4	17.4	14.5	10.0	10.4	46.8	...	...	...	...	...	...	...	...
11	—	4.5	66.4	17.3	21.8	26.4	9.0	—	—	5.6	30.6	9.9	12.5	—	15.6	13.5
12	—	—	35.8	27.0	18.0	19.8	57.2	—	—	3.8	—	—	10.4	8.0	20.4	—
13	5.6	11.7	59.2	4.4	15.2	9.6	29.7	28.5	5.5	6.0	35.0	20.0	—	7.5	—	5.6
14	13.2	7.0	62.4	20.7	22.4	15.3	41.8	—	...	...	...	...	...	...	...	—
Average.....	12.4	13.1	52.6	16.5	19.0	24.4	35.5	26.3	14.8	13.7	37.7	32.5	33.5	13.2	21.6	18.1
Range.....	5.6-30.0	4.5-24.6	23.5-66.4	3.6-33.8	10.5-47.7	9.2-60.0	7.2-80.0	4.0-59.9	3.7-30.0	3.8-43.5	12.6-79.0	9.9-80.9	8.9-69.8	1.6-23.9	1.4-40.4	4.2-39.4

ten minute period, reaching a level less than that noted before stimulation in 11 of the 13 cases. The concentration fell to less than 1 cc. of tenth-normal potassium hydroxide in every case in the second ten minute period. The concentration of trypsin remained at less than prestimulation levels in 9 of 11 cases in the third period and in 6 of 12 in the fourth period. The concentration of trypsin in terms of cubic centimeters of tenth-normal potassium hydroxide per cubic centimeter of duodenal contents was 1 or less in every case during the third period. The lowest concentration was obtained in 9 of 13 cases in the second, in 3 of 13 in the third and in 1 of 13 in the fourth ten minute period. Although the concentration tended to remain at less than prestimulation levels, a rise greater than that in the second ten minute period usually occurred in the third and fourth periods. The concentration did not return to prestimulation levels during the course of the experiment in 10 of the 13 cases. Secretin produces a prolonged depression of the concentration of trypsin, lasting, as a rule, throughout the experiment but greatest in the second ten minute period; the depression is usually followed by a slight secondary rise which usually does not reach prestimulation levels.

Mecholyl chloride produced a contrasting effect. After stimulation with this drug (table 4), the concentration increased in every case, the increase varying from a fraction to fourfold. The concentration of trypsin, in terms of cubic centimeters of tenth-normal potassium hydroxide per cubic centimeter of duodenal content, exceeded 3 cc. in 5 cases and 2.5 cc. in 9 of 10 cases at some time during the poststimulation period. The maximal increase occurred three times in the first period and twice in the second, third and fourth periods, respectively. An increase occurred in the first ten minute period in 8 of 9 cases; a concentration greater than prestimulation levels was maintained in all cases in the second ten minute period, in 6 of 8 cases in the third ten minute period and in 7 of 9 cases in the fourth ten minute period. The increase persisted at greater than prestimulation levels for twenty minutes in 1 case, thirty minutes in 1 case, forty minutes in 3 cases, forty to sixty minutes in 3 cases and sixty to eighty minutes in 1 case. Mecholyl produces a prolonged rise in concentration of trypsin, in terms of cubic centimeters of tenth-normal potassium hydroxide per cubic centimeter of duodenal contents, levels greater than those before stimulation persisting sixty to eighty minutes (chart 5).

Total Amount of Trypsin.—Before stimulation, the total value for trypsin per unit of time, in terms of cubic centimeters of tenth-normal potassium hydroxide per cubic centimeter of duodenal contents, varied from 3.7 to 43.5 cc. and averaged 13.4 cc. (table 4). After stimulation with secretin, a rapid rise in the total trypsin per unit of time occurred in all 13 cases, varying from a fraction to sixteenfold and averaging fourfold; the total value for trypsin varied between 23.5 and 66 cc. during the first ten minute period. The maximal increase occurred in 12 of the 13 cases in the first period. The rapid rise in total trypsin was followed by a rapid fall in the second period in all 13, the value reaching lower than prestimulation levels in 6 of 8 cases. The fall in total trypsin was followed by a slight rise in 8 of 11 cases in the third and fourth ten minute periods. Again, it is to be emphasized that the only significant increase in the total values for trypsin occurred in the first ten minute period, when the concentration of trypsin had felt only partially the depressing effect of secretin and when the stimulating effect of secretin on volume was at its height.

After stimulation with mecholyl chloride a rise in total trypsin occurred in every case, varying from twofold to sixfold, and averaging threefold (table 4). The maximal increase occurred in 6 cases in the first, in 1 case in the second and in

2 cases in the third ten minute period; the total trypsin value returned to prestimulation levels in 1 case in the third, in 5 cases in the fourth ten minute period, in 1 case in the first and in 2 cases in the second twenty minute period. In 1 case the increase in total trypsin to values greater than those before stimulation persisted throughout the eighty minutes. The greatest total value for trypsin in terms of cubic centimeters of tenth-normal potassium hydroxide per ten minute period during the first four ten minute periods after stimulation with mecholyl chloride varied between 20 and 80 cc., a range of values similar to that found during the first ten minute period after stimulation with secretin. Mecholyl chloride produced a marked increase in the total values for trypsin per unit of time which persisted in general throughout the first thirty minutes, reaching prestimulation levels some time between forty and eighty minutes after stimulation, contrasting with the rapid increase in the first ten minute period following stimulation with secretin that in turn is followed by a rapid fall near prestimulation levels (chart 6).

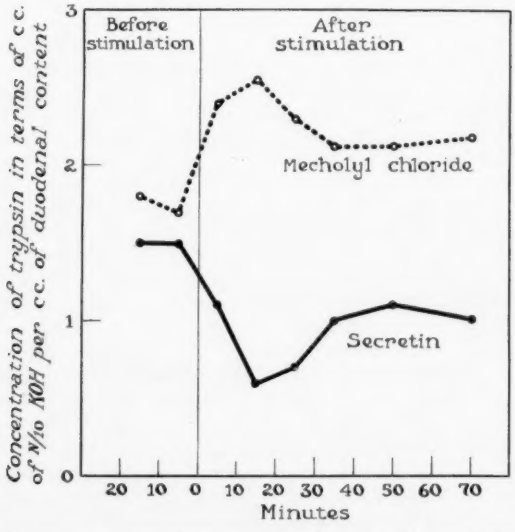

Chart 5.—Average concentration of trypsin per cubic centimeter of duodenal contents in samples obtained per unit of time before and after stimulation with secretin and mecholyl chloride.

Concentration of Lipase.—Before stimulation, the concentration of lipase in terms of cubic centimeters of twentieth-normal sodium hydroxide per cubic centimeter of duodenal juice varied between 2 and 267 cc. and averaged 76 cc. (table 5). After stimulation with secretin, the concentration fell below prestimulation levels in 10 of the 13 cases during the first or second ten minute period, whereas a rise from the level of the second ten minute period occurred in 10 cases in the third ten minute period. The lowest concentration was obtained in 5 cases in the first and in 6 cases in the second ten minute period. A return to prestimulation levels occurred in 1 case in twenty minutes, in 3 cases in thirty minutes, in 1 case in forty minutes and in 1 case in eighty minutes; in 3 cases there was no return to

TABLE 5.—*Lipase Concentration Before and After Stimulation with Secretin and Mecholyl Chloride (Cubic Centimeters of Twentieth-Normal Sodium Hydroxide per Cubic Centimeter of Duodenal Contents)*

	Before Secretin, 10 Minute Periods		After Secretin						Before Mecholyl Chloride, 10 Minute Periods		After Mecholyl Chloride					
			10 Minute Periods				20 Minute Periods				10 Minute Periods				20 Minute Periods	
Case	2	1	1	2	3	4	5	6	2	1	1	2	3	4	5	6
1	78	—	100	57	—	—	93	90	...	...	...	...	...	...	...	...
2	267	95	50	425	121	105	69	71	97	107	122	111	123	136	143	100
3	137	81	37	37	115	129	85	87	56	78	82	75	78	41	62	72
4	...	...	...	...	...	...	...	...	—	6	67	94	39	34	28	71
5	49	83	2	1	23	2	9	89	...	...	...	...	...	...	...	...
6	5	108	60	62	76	49	52	41	77	64	75	91	97	70	113	119
7	39	85	101	101	104	108	109	140	61	79	82	78	112	104	138	86
8	132	128	103	85	44	52	62	96	84	98	116	106	—	164	163	—
9	94	105	88	81	95	89	87	98	...	...	...	...	...	...	...	...
10	17	65	30	90	102	95	93	94	...	...	...	...	...	...	...	...
11	—	112	65	77	104	81	64	—	—	2	61	88	128	161	129	101
12	—	—	91	64	79	85	91	—	—	5	—	—	98	124	112	—
13	26	14	170	26	50	74	183	73	66	64	95	154	—	200	—	152
14	36	62	64	82	80	75	80	—	90	95	95	121	109	150	140	100
Average.....	81	85	74	62	83	79	83	88	76	60	88	102	98	118	114	100
Range.....	5.5-	14.5-	2-	1-	23-	2-	9-	41-	56-	2-	61-	78-	39-	34-	28-	71-
	267	128	170	101	121	129	183	140	97	107	122	154	128	200	143	152

Lipase per Total Sample Before and After Stimulation with Secretin and Mecholyl Chloride (Cubic Centimeters of Twentieth-Normal Sodium Hydroxide per Total Sample)

1	1,560	—	3,200	1,026	—	—	1,860	1,260	...	...	...	...	...	...	...	...
2	3,204	1,330	930	1,058	2,904	2,568	2,365	1,182	941	1,390	2,554	4,030	3,066	680	2,448	1,289
3	1,096	890	2,033	2,116	6,095	5,547	4,941	2,321	557	1,178	1,968	1,251	1,722	532	1,217	1,216
4	...	...	...	...	...	...	...	...	—	42	469	611	819	374	252	461
5	147	664	126	18	345	50	459	1,424	...	...	...	...	...	...	...	...
6	54	1,944	3,042	1,180	1,203	1,850	1,608	340	770	282	1,048	923	477	292	1,243	952
7	117	712	2,275	2,920	2,908	3,730	4,360	4,480	146	626	670	836	626	104	69	258
8	792	—	4,683	2,928	2,464	1,315	2,158	976	592	719	2,169	954	—	1,148	1,793	—
9	940	1,365	2,728	1,944	4,465	1,869	783	490	...	...	...	...	...	...	...	...
10	119	715	960	2,610	2,958	2,375	2,418	3,666	...	...	...	...	...	...	...	...
11	—	560	2,848	1,811	2,294	2,236	384	—	—	16	1,098	264	640	2,093	774	505
12	—	—	2,957	1,920	1,580	1,530	4,004	—	—	12	—	—	784	620	1,904	—
13	1,060	94	6,290	572	950	888	4,841	1 387	363	256	1,330	1,232	—	630	—	608
14	396	434	3,328	1,886	2,240	1,275	3,040	—	630	665	1,235	1,331	1,526	1,500	420	200
Average.....	862	811	2,723	1,691	2,534	2 103	2 569	1,753	571	549	1,393	1,270	1,207	794	1,124	686
Range.....	54-	94-	126-	18-	345-	50-	384-	340-	146-	12-	670-	264-	632-	104-	69-	200-
	3,204	1,944	4,680	2,928	6,095	5,547	4,940	4,480	941	1,390	2,554	4,030	3,066	2,093	2,448	1,289

prestimulation levels. A glance at the figures in table 5 will show that whereas there was a tendency toward a fall after stimulation with secretin, the tendency was not nearly so marked or so precise as it was in the case of amylase or trypsin.

After stimulation with mecholyl chloride an increase in the concentration of lipase occurred in 9 of 10 cases; the increase varied from 25 to 65 per cent (table 5). The maximal concentration occurred in 1 case in the first, in 1 case in the second, in 5 cases in the fourth, in 2 cases in the fifth and in 1 case in the sixth period after stimulation. A concentration greater than that before stimulation was maintained for forty minutes in 9 of the 10, for sixty minutes in 8 of 9 and for eighty minutes in 6 of 8 subjects. In short, a prolonged rise to greater than prestimulation levels, persisting sixty to eighty minutes, occurred after stimulation with mecholyl chloride. Although this rise was not so marked as in the case of trypsin and amylase, the tendency is well seen and is in contrast with the behavior of concentration of lipase after stimulation with secretin (chart 7).

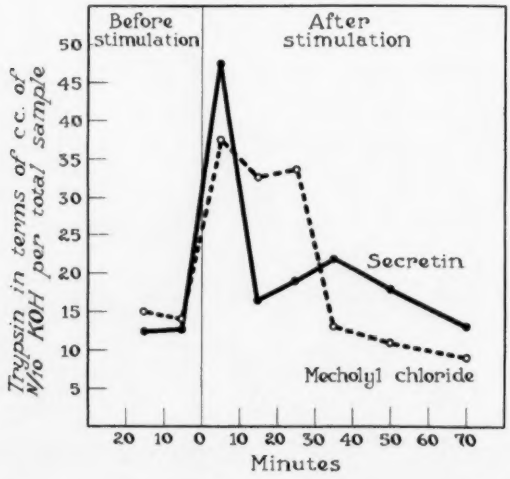

Chart 6.—Average value for total trypsin per total sample obtained per unit of time before and after stimulation with secretin and mecholyl chloride.

Lipase per Total Sample.—Before stimulation, the total value for lipase in the duodenal contents collected in a ten minute period, in terms of cubic centimeters of twentieth-normal sodium hydroxide, varied from 12 to 3,200 cc. and averaged 700 cc. (table 5). After stimulation with secretin, the lipase per total sample increased rapidly in 11 of 13 cases, varied from one-half to thirtyfold in the 11 cases and averaged three and a half times the prestimulation value. A slight decrease occurred in 2 of the 13 cases. The greatest increase occurred when prestimulation levels were low. The maximal increase occurred in the first ten minute period in 7 cases, in the third ten minute period in 2 cases and in the fourth ten minute period in 2 cases; a fall occurred in the second ten minute period in 8 and was followed by a secondary rise in only 3 of the 8 cases. The total amount returned to prestimulation levels in 2 cases in the fourth ten minute period, in 3

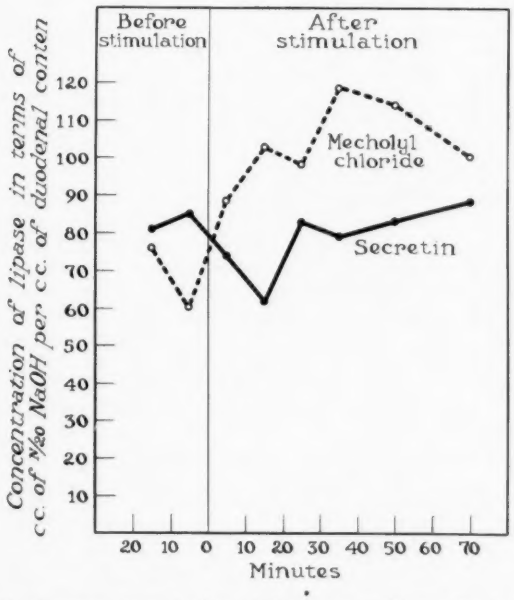

Chart 7.—Average concentration of lipase per cubic centimeter of duodenal contents in the sample obtained per unit of time before and after stimulation with secretin and mecholyl chloride.

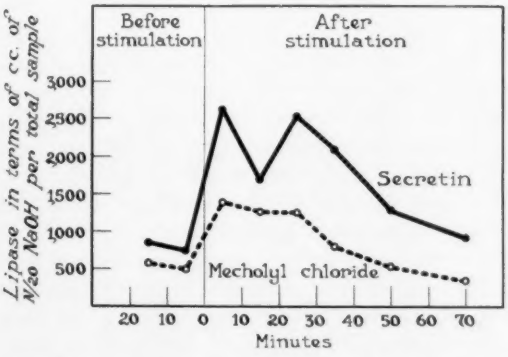

Chart 8.—Average value for total lipase per sample obtained during the unit of time before and after stimulation with secretin and mecholyl chloride.

cases in the first twenty minute period and in 2 cases in the second twenty minute period but persisted above prestimulation levels in 4 cases during the course of the experiment. In 12 of 13 cases a figure of more than 2,500 cc. was reached at some time during the period after stimulation. Secretin produces a rapid increase in the total value for lipase, the maximal increase usually occurring in the first ten minute period. The increase is much more prolonged than in the case of amylase and trypsin. The total value returns to prestimulation levels in the forty to eighty minute period, or later.

After stimulation with mecholyl chloride an increase in the total value for lipase per unit of time in terms of twentieth-normal sodium hydroxide occurred in all 10 cases, varying from one-half to one hundred and fifty times the original value, depending to a considerable extent on the presecretory levels; the maximal increase occurred in the first ten minute period in 5 cases, in the second ten minute period in 2 and in the third ten minute period in 3 (table 5). The total value for lipase returned to prestimulation levels in 1 case in the third and in 4 in the fourth ten minute period but persisted beyond forty minutes in half of the subjects,[14] returning to prestimulation levels in 2 cases in forty to sixty minute intervals but persisting beyond eighty minutes in 3 cases. It is to be noted that in all these 3 cases the prestimulation levels were very low. Mecholyl chloride produces a marked increase in the total value for lipase, averaging two and a half times the original value, that persists throughout the first three ten minute periods, reaching prestimulation levels in the thirty to forty minute or forty to sixty minute period (chart 8).

SUMMARY AND CONCLUSIONS

Continuous suction through a double tube has been used in the study of pancreatic secretion in man after stimulation with (1) secretin and (2) mecholyl chloride. The tube was composed of two lumens. When in correct position, one lumen opened into the stomach for removal of gastric contents and for prevention of entrance of gastric contents into the duodenum; the other lumen opened into the duodenal cavity for the removal of duodenal contents. The method has proved mechanically satisfactory for this purpose.

Secretin and mecholyl chloride produced contrasting effects on pancreatic secretion. Secretin produced a large volume of duodenal contents, increased the p_H values and effected a prolonged reduction in the concentration of enzymes. Mecholyl chloride, on the other hand, increased the volume of duodenal contents only slightly, did not appreciably affect the p_H values and provoked a prolonged increase in the concentration of enzymes.

Although the total value for the several enzymes per unit of time was increased by both secretin and mecholyl chloride, the increase in the total value for amylase and trypsin following stimulation with secretin occurred almost entirely during the first ten minute period after stimulation but was prolonged for thirty minutes or longer after stimulation with mecholyl chloride. The increase in total value for these enzymes appeared to be due to a washing-out process in the case

of secretin but was due to an active secretion of enzymes in the case of mecholyl chloride. The total value for lipase was likewise increased after each type of stimulant was given, but the increase was more prolonged after stimulation with secretin than were the total values for amylase and trypsin. The significance of this different type of behavior is not clear.

Stimulation with secretin demonstrated that the pancreas is capable of secreting a large volume of highly alkaline juice. Even the increase in total value for the enzymes secreted during the first ten minute period after stimulation was more of a measure of capacity of the pancreas to secrete a large volume of pancreatic juice than of its capacity for secreting enzymes. Stimulation with mecholyl chloride, on the other hand, demonstrated that the pancreas is able to secrete a juice rich in enzymes. As in animals, the humoral mechanism in man produces an effect on pancreatic secretion which differs from that produced by the vagal mechanism.

The effects of secretin and mecholyl chloride on pancreatic secretion follow a definite pattern; they vary, however, in magnitude from one experiment to another but to a lesser degree when multiple tests are performed on the same subject. After stimulation with secretin, the concentration of amylase in terms of grams of maltose per cubic centimeter of duodenal contents fell usually below 0.5 Gm. of maltose, and the concentration of trypsin in terms of twentieth-normal potassium hydroxide per cubic centimeter of duodenal contents, to less than 1 cc. After stimulation with mecholyl chloride, the concentration of amylase usually reached 3.7 Gm., and that of trypsin, 2.5 cc.

After stimulation with secretin, the total value for the first ten minute period in the case of amylase varied from 10 to 100 Gm., and in the case of trypsin, from 20 to 70 cc.; the value for lipase during the same period varied from 100 to 6,000 cc., as measured in terms of twentieth-normal sodium hydroxide. After stimulation with mecholyl chloride, the highest total values per unit of time following stimulation varied from 14 to 125 Gm. of maltose per ten minute period in the case of amylase, from 10 to 80 cc. of tenth-normal potassium hydroxide per ten minute period in the case of trypsin and from 1,100 to 4,000 cc. of twentieth-normal sodium hydroxide per ten minute period in the case of lipase. The fluctuations in total values per unit of time result from both the variations in the volume of duodenal contents obtained and the variations in the concentration of enzymes and occur at least in part because of the mechanical difficulties inherent in the quantitative removal of the duodenal contents.

Both concentrations and total values for enzymes should be used in determining pancreatic function. However, because the variations in the

total values for normal persons after stimulation with both secretin and mecholyl chloride have proved to be greater than the variations in the concentrations after stimulation with mecholyl chloride, the concentrations after stimulation with mecholyl chloride may prove to be a more reliable index of pancreatic function than the total values per unit of time after stimulation with either secretin or mecholyl chloride.

The proper exploration of pancreatic function demands investigation of both the humoral and the vagal mechanism of control of pancreatic function.

Progress in Internal Medicine

VASCULAR DISEASES

A REVIEW OF SOME OF THE RECENT LITERATURE, WITH A CRITICAL REVIEW OF THE SURGICAL TREATMENT

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REVIEW OF SOME OF THE RECENT LITERATURE

BY DR. VAN DELLEN AND DR. SCUPHAM

In these reviews of the past six years we have not attempted to include all of the available literature on vascular diseases. Many deserving articles have undoubtedly been missed, and consequently the reviews must not be considered complete. Preference was usually given to articles containing original ideas, as well as to those confirming or disproving existing beliefs. Many articles were included on merit alone, or their contents were thought worthy of repetition. The study of vascular diseases is not without its difficulties and is open to criticism. The vast amount of instrumentation is certainly unnecessary for diagnosis; in the majority of cases the history and findings alone are sufficient. Arteriosclerosis, the most prevalent vascular disease, has received too little attention.

Three monographs dealing with diseases of the peripheral vessels were published during the past year. Of the three, Homans' [1] is probably the most complete, with ample discussion on disorders of the arteries, veins and lymphatics. Conservative and radical forms of therapy are adequately outlined, with numerous illustrations of important aids in diagnosis and treatment. Although certain established procedures are

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1. Homans, J.: Circulatory Diseases of the Extremities, New York, The Macmillan Company, 1939.

not included, one is not wanting in sufficient armamentarium to treat adequately the majority of patients. In the monograph by Ochsner and Mahorner [2] the bulk of material is devoted to venous disorders. These authors covered the subject of varicose veins in a concise and authoritative manner, with the help of excellent diagrams and photographs. The history of the treatment of varicose veins is included, as well as a review of the anatomy, pathology, physiology, etiology, clinical aspects, examination and treatment. Collens and Wilensky [3] more closely adhered to the subject of peripheral arterial disturbances. Many necessary surgical procedures, as well as congenital anomalies, aneurysms and varicose veins, are not discussed. Too much detail is allotted to certain tests and apparatus of the authors, while others equally as important are less favorably treated.

Saland and his colleagues [4] suggested criteria for the classification and diagnosis of peripheral vascular diseases, based on the diagnostic criteria for heart disease published by the Heart Committee of the New York Tuberculosis and Health Association. No claim was made by the authors that these represented ultimate and immutable principles. This was wise, as many of the statements are open to question. It was suggested that a comprehensive diagnosis of peripheral vascular disease should include a statement of (*a*) the etiologic agent or agents; (*b*) the anatomic status; (*c*) the extent of physiologic impairment and (*d*) the functional capacity of the patient. The names of all the diseases are listed under the etiologic agent or agents, with the criteria for diagnosis in each case. To reach an anatomic diagnosis one uses tests to ascertain whether the vessel is organically or functionally closed and the effect of such closure on the surrounding tissues. The physiologic changes refer mainly to the symptoms, amount of spasm and vascular reserve, which again reverts to the amount of spasm and the capacity for dilatation. The functional diagnosis is similar to that of heart disease. Such a classification is desirable and is a step in the right direction. It is, however, difficult of application because, in the present state of knowledge, the etiologic factors in many vascular disorders are uncertain. The disorders themselves are syndromes rather than disease entities. As an example, erythromelalgia occurs as a symptom of several diseases, including arteriosclerosis and polycythaemia vera.

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2. Ochsner, A., and Mahorner, H.: Varicose Veins, St. Louis, C. V. Mosby Company, 1939.

3. Collens, W. S., and Wilensky, N. D.: Peripheral Vascular Diseases: Diagnosis and Treatment, Springfield, Ill., Charles C. Thomas, Publisher, 1939.

4. Saland, G.; Klein, C.; Zurrow, H.; Gootnick, A., and Katz, A.: Criteria for the Classification and Diagnosis of Peripheral Vascular Diseases, Arch. Int. Med. **65**:1035 (May) 1940.

PHYSIOLOGY

Roth, Horton and Sheard [5] continued their studies on the role of the extremities in the dissipation of heat. Data were obtained from 2 normal subjects. It was shown that relative humidity had little effect on the cutaneous temperatures of the body, as indicated by changes in the temperature of the fingers and toes. Studies were made when the body was subjected to fixed environmental temperatures ranging from approximately 23 to 28 C. (73.4 to 82.4 F.), with a fairly wide range (35 to 75 per cent) of relative humidity. They expressed the opinion that minor increases in cutaneous temperature which might be produced by large increases in atmospheric humidity were overshadowed by the relatively large thermal changes in the extremities due to small changes in environmental temperatures. They concluded that under these conditions the dissipation of heat from the body is dependent chiefly on the environmental temperature and is little influenced by relative humidity. Sheard, Horton and Williams [6] studied the rates of cooling and warming under normal circulatory conditions and in peripheral vascular diseases. The data obtained from a group of normal persons were subjected to mathematical analysis. They found the rate of cooling, in each instance, to be rather constant, ranging from 0.02 to 0.05 C. (0.36 to 0.09 F.) per minute. Patients with peripheral vascular disease gave a similar response. This is logical since, if account is taken of the metabolic rates, the rates of cooling of the toes are the same under normal circulatory conditions and in peripheral vascular disease, vasoconstriction, whether spastic or obstructive, being operative in both.

In contrast, the rate of warming was found to differ in normal and in pathologic states. In normal persons two distinct rates were noted. The initial rates were found to be between 0.015 and 0.03 C. (0.027 and 0.054 F.) per minute and were constant until the temperature of the toes reached a value of 27 to 28 C. (80.6 to 82.4 F.). At this stage the rate became faster, lying between 0.04 and 0.10 C. (0.072 and 0.18 F.) per minute. The initial rate was considered to represent only the rate of environmental heating of the tissue, whereas the second rate showed the combined effects of the heating of tissue by the environment and the increased supply of blood brought to the tissue. In cases in which abnormal vasoconstriction or organic occlusion was present the initial rate of heating was found to be similar to that of normal persons.

5. Roth, G. M.; Horton, B. T., and Sheard, C.: The Relative Roles of the Extremities in the Dissipation of Heat from the Human Body Under Various Environmental Temperatures and Relative Humidities, Am. J. Physiol. **128**:782 (March) 1940.

6. Sheard, C.; Horton, B. T., and Williams, M. M. D.: Rates of Cooling and Warming of the Extremities in Normal Circulatory Conditions and in Peripheral Vascular Diseases, Proc. Staff Meet., Mayo Clin. **14**:541 (Aug. 23) 1939.

On the other hand, in the range of environmental temperatures in which vasodilatation occurred normally, there were abnormally low or definitely decreased rates of warming. In many cases of essential hypertension similar responses were given, showing a considerable degree of vasoconstriction. In cases of thromboangiitis obliterans the initial rate of warming generally was near the lowest limit for normal circulation, namely, 0.015 C. (0.027 F.) per minute. In some instances a slight increase took place after the temperature of the toes reached values of from 29 to 30 C. (84.2 to 86 F.), but in many the rate decreased after this level had been reached.

Nielsen, Herrington and Winslow [7] studied the effect on the peripheral circulation of a passive change in body posture in persons subjected to high environmental temperatures. Observations were made on patients lying on a tilting table at room temperatures of 30 and 35.6 C. (86 and 96.1 F.). After the change in posture from the horizontal to the "feet-down" position (45 degrees from horizontal), the rectal and toe temperatures were increased and the peripheral cutaneous temperature was decreased. The peripheral constriction increased with progressively higher environmental temperatures and higher angles of tilting. A tendency to collapse was not uncommon when both the environmental temperatures and the angles of tilting were greatly increased. The rise in rectal temperature was roughly proportional to the degree of vasoconstriction in the extremities. This was thought to be functionally associated with the stimulus to increased evaporation resulting from disturbance in heat regulation when peripheral vasoconstriction took place. The authors expressed the opinion that the vasoconstriction in the skin with the patient in the vertical position was related to the effect of gravity on the circulation, particularly in persons with decreased venous return and cardiac output. This appeared as a logical assumption, as Asmussen, Christensen and Nielsen [8] had previously shown that the decrease in cardiac output was compensated by vasoconstriction in such organs as the intestines and kidneys.

Blood Flow.—Wright and Phelps [9] stated that in spite of the many advantages of the plethysmographic method of Hewlett and Van Zwaluwenburg for determining blood flow in the limbs, and even more of its modification by subsequent workers, it has a number of hidden

7. Nielsen, M.; Herrington, L. P., and Winslow, C.-E.: The Effect of Posture upon Peripheral Circulation, Am. J. Physiol. **127**:573 (Oct.) 1939.

8. Asmussen, E.; Christensen, E. H., and Nielsen, M.: Ueber die Kreislaufinsuffizienz in stehender Stellung bei normalem arteriellen Druck und herabgesetztem Minutenvolumen, Skandinav. Arch. f. Physiol. **81**:214, 1939.

9. Wright, G. W., and Phelps, K.: A Comparison of Procedures for Increasing Blood Flow to Limbs Using an Improved Optical Plethysmograph, J. Clin. Investigation **19**:273 (March) 1940.

faults which lead to inaccuracies in the estimation of flow under various conditions. Among these are the yielding diaphragm surrounding the limb and closing the plethysmograph, displacement of fluid into the plethysmograph by inflation of the collecting cuff and lack of sensitivity of the entire apparatus.

The authors then described a boot plethysmograph which is easy to apply and calibrate, the open end of which is sealed around the leg without constriction by the use of plaster of paris and hard paste of zinc oxide, and which is comfortable for prolonged periods of study. The apparatus is connected with a Frank segment capsule, giving the entire system frequencies up to 100 per second.

To obviate the artefacts incurred through displacement of fluid into the plethysmograph by the inflated cuff, an arrangement of stopcocks is provided by which the collecting cuff is inflated while the plethysmograph and recording capsule remain open to the atmosphere, but exactly one second later the system is automatically closed and the changes in volume are recorded. The rise of a full pulse beat starting exactly one and six-tenths seconds after inflation is used to measure the net flow per cycle. From this, volume flow per minute per hundred cubic centimeters of leg substance is calculated in the conventional manner.

The phasic arterial blood flow of the leg recorded in this way for normal subjects at rest in a warm room (28 to 30 C. [82.4 to 86 F.]) showed three distinct variations during each cycle: (1) a rapid systolic forward flow; (2) a slower, smaller and variable systolic backflow, and (3) a slow forward diastolic flow. The net arterial inflow depends not only on phase 1 plus phase 3 but also on the amount subtracted from phase 2. All of these varied under different circumstances. Since only the amplitude (phase 1) of the pulse volume is recorded by plethysmographs or oscillometers, these methods give no quantitative estimate of changes in volume flow, and under some conditions they do not show even the correct directional changes.

The resting flow determined by the procedure described by the authors remained constant within approximately 6 per cent of the mean during repeated determinations within an hour. It varied greatly in different persons or in the same person from day to day unless strictly basal conditions were observed.

A study of various procedures suggested for promoting a maximal blood flow in the leg showed that direct application of heat and sciatic nerve block were the most efficacious. Application of heat to both upper extremities (reflex heat) produced an effect only about one half as great. Wright and Phelps were unable to detect any increase in blood flow after effective spinal anesthesia or sacral diathermy.

Other procedures which affected the heart rate or blood pressure significantly influenced blood flow in a variable manner. Amyl nitrite,

for example, increased the amplitude of oscillations, but often caused an actual decrease in volume flow.

Burton [10] studied the momentary fluctuations in the blood flow to the fingers. He used a simple finger plethysmograph adapted to measure volume pulsations at six second intervals. He found these fluctuations to be rhythmic and to consist of two main components, namely: a respiratory fluctuation of small amplitude and a periodic constriction of slower rhythm and large amplitude. These were noted to be simultaneous in all digits and were accompanied by cardiac acceleration and rise of blood pressure, indicating activity of the entire peripheral sympathetic system.

Burton also noted that the rhythm was modified by factors in temperature regulation. The amplitude of the waves was greatest at the middle ranges of rates of blood flow and at lower temperatures, being less during dilatation and least during constriction. The frequency of the rhythm was also modified by the same factors, being greatest with cooler temperatures and lower values for rate of blood flow.

Burton expressed the opinion that the tremendous range of rates of blood flow is made possible by the arteriovenous anastomoses and represents not a metabolic need but a purely mechanical means of assisting regulation of temperature by elimination of body heat. This is accomplished, therefore, not by allowing the peripheral blood flow to assume an appropriate steady level but by the adjustment of an average flow which fluctuates rhythmically between high and low values.

Mann, Herrick, Essex and Baldes [11] studied the flow of blood in vessels in which the lumen was mechanically constricted. These studies were made on the carotid artery of dogs, the constricting units being less than 1 cm. in length. The lumen had to be constricted to a considerable degree before the blood flow was significantly reduced. The results were expressed in terms of the reduction in external diameter, internal diameter and area of the lumen. The external diameter could be reduced 40 per cent without any significant reduction in blood flow, but when it was reduced as much as 60 per cent the blood flow decreased 49 per cent. On the other hand, the internal diameter could be reduced 70 per cent before a 50 per cent reduction in blood flow took place. When stated in terms of the area of the lumen the results were more striking. The area of the lumen could be reduced 50 per cent without any change in blood flow, and could be reduced as much as 90 per cent before a 50 per cent reduction in blood flow occurred.

10. Burton, A. C.: The Range and Variability of the Blood Flow in the Human Fingers and the Vasomotor Regulation of the Body Temperature, Am. J. Physiol. **127**:437 (Oct.) 1939.

11. Mann, F. C.; Herrick, J. F.; Essex, H. E., and Baldes, E. J.: Effect on Blood Flow of Decreasing Lumen of Blood Vessel, Surgery **4**:249 (Aug.) 1938.

Circulation Time.—Kvale and Allen [12] studied in greater detail the solution introduced by Spier, Wright and Saylor for study of the circulation time. This fluid consists of a physiologic solution of sodium chloride containing calcium gluconate and magnesium and cupric sulfate. The circulation was timed by the occurrence of a warm sensation in the tongue, perineum, hands and feet following the intravenous injection of the solution. A "blank" was recorded when no sensation was felt in one area or another. The use of this solution was found to be a safe and good method, as it fulfilled the usual qualifications for fluids of this type. The authors, however, were unable to show any evidence that the sensation of warmth produced in the throat, hands, perineum and feet indicated that the fluid had arrived in these areas. They agreed that a reaction time must occur, which may be variable, thus influencing the results, and that consequently the figures obtained were valid only for comparative purposes.

Average values were obtained on normal subjects under controlled conditions. The ranges in time increased, being least in the "arm to tongue" time and greatest in the "arm to foot" time. Wide ranges in time demonstrated that the speed of blood flow varies widely in the same person under different conditions, but that under similar and basal conditions the velocity of flow is remarkably constant.

In cases of thromboangiitis obliterans and arteriosclerosis obliterans the speed of blood flow to the hands and feet was usually diminished, depending on the degree of vascular obliteration. Inconsistency of results led the authors to conclude that this test for circulation time could not be used in diagnosis of occlusive arterial disease. In cases of hyperthyroidism the speed of flow of blood was increased in the arteries as well as in the veins.

"Ventricle to perineum" circulation time was calculated by subtracting the "arm to tongue" time from the "arm to perineum" time. Similarly, the "arm to hand" time minus the "arm to tongue" time equaled the "ventricle to hand" time, and the "arm to foot" time minus the "arm to tongue" time, the "ventricle to foot" time. Although these "times" were assumed, they furnished the first means of calculating the velocity of arterial blood flow in man.

Berk [13] made similar observations on circulation time, using 5 cc. of a 10 per cent solution of magnesium sulfate. Circulation times were determined on 200 normal persons and on 21 patients with peripheral vascular diseases. Berk studied the "arm to hand" and the "arm to

12. Kvale, W. F., and Allen, E. V.: The Rate of the Circulation in the Arteries and Veins of Man: I. Studies of Normal Subjects and Those with Occlusive Arterial Disease and Hyperthyroidism, Am. Heart J. **18**:519 (Nov.) 1939.

13. Berk, J. E.: Circulation Time (Magnesium Sulfate Method) in the Diagnosis of Peripheral Vascular Disease, Am. J. M. Sc. **199**:505 (April) 1940.

foot" time. His figures were considerably higher than those obtained by Kvale and Allen, as well as other authors, in this type of test. As in the previous article, the readings for patients with peripheral vascular diseases exhibited a tendency toward a longer circulation time, as well as an increase in the number of "blanks."

Kvale and Allen [14] also studied the influence of various physiologic factors on the circulation time, using the same method. During digestion the speed of blood flow was found to be increased. The speed of circulation to the feet was decreased when a patient stood erect. This was thought to be due to vasoconstriction which occurred on standing. Exercise increased the speed of circulation. Marked rises in pulse rate, without affecting the blood pressure significantly, and with little or no effect on the temperature of the skin, increased the velocity of blood flow. Minor variations in pulse rate had no effect on the velocity of flow. The authors also noted that the velocity of the flow of blood in the peripheral arteries of man dependent on the cutaneous temperature. Increasing the temperature increased the speed of flow, and decreasing the temperature decreased the speed of flow. The latter findings are in accord with those of Stead and Kunkel,[15] who showed that the blood flow of an extremity varied with changes in the local temperature of that extremity. In 6 subjects the "elbow to carotid sinus" circulation time was measured by means of injection of a solution of sodium cyanide in each arm. The two upper extremities were kept at different temperatures by immersing one hand in water at 23 to 30 C. and the other in water at 40 to 43 C. The circulation time in the cool arm averaged thirty-two and three-tenths seconds and that in the warm arm eighteen and five-tenths seconds. Incidentally, these circulation times for sodium cyanide were slower than those of Kvale and Allen [16] for similar distances. The latter authors made note of this in comparing the two methods. By mixing a solution of sodium cyanide with the solution they used and injecting this mixture into the cubital vein, they showed that there was an error in the sodium cyanide method. The time required for blood to flow from an arm vein to the carotid sinus as ascertained by injection of a solution of sodium cyanide, appeared to be about three seconds more than the time actually required for blood to flow from an arm vein to the tongue.

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14. Kvale, W. F., and Allen, E. V.: The Rate of the Circulation in the Arteries and Veins of Man: III. The Influence of Temperature of the Skin, Digestion, Posture and Exercise, Am. Heart J. **18**:546 (Nov.) 1939.

15. Stead, E. A., Jr., and Kunkel, P.: Influence of the Peripheral Circulation in the Upper Extremity on the Circulation Time as Measured by the Sodium Cyanide Method, Am. J. M. Sc. **198**:49 (July) 1939.

16. Kvale, W. F., and Allen, E. V.: The Rate of the Circulation in the Arteries and Veins of Man: IV. An Error in the Sodium Cyanide Method of Determining Speed of Venous Blood Flow, Am. Heart J. **18**:557 (Nov.) 1939.

In a later publication, Kvale, Smith and Allen [17] reviewed all the foregoing material. In addition, they showed that the speed of flow of blood after an operation is usually reduced in the veins of the lower extremities. In the "arm to tongue" circulation time the decrease was noted after the first forty-eight hours, but the time then increased until the thirteenth postoperative day.

Velocity of Pulse Wave.—Matthes, Gross and Goepfert [18] studied the pulse wave in the arteries of the upper extremity. The speed of the pulse wave in most of the arteries (wrist to tip of finger) was considerably lower than that in the medium arteries (cubital to radial region). The authors thus assumed an air chamber action of the most peripheral arteries. They concluded that the peripheral volume pulse is a fluctuation of the blood content of the small and smallest arteries of the skin, as capillaries and venules do not pulsate. Variations in the blood content of these vessels were found to occur especially in arrythmias of the heart, making characteristic patterns.

Capillaries.—Clark and Clark [19] observed the growth of blood capillaries in the adult rabbit. Microscopic studies in which the finest details were observed with great clearness demonstrated that new blood vessels arise by a process of capillary sprouting from preexisting vascular endothelium and that the endothelium of the growing vessels remains specific. The authors showed that the regenerating capillaries of the rabbit resembled in their manner of growth, through anastomoses with neighboring vessels and lumen formation, the growing capillaries of the amphibian larvae.

Cells resembling fibroblasts were observed to adhere to the walls of newly formed capillaries, remaining as adventitial cells. The tissue outside growing capillaries in the transparent chamber underwent characteristic changes as the new vessels advanced and received a blood supply. Fibrin dissolved, and the extravascular fluid changed to a tissue substance resembling a soft gel. Subsequently the fibroblasts migrated into the growth space, and connective tissue fibers formed between the new capillaries.

Capillary growth occurred rapidly and was most abundant in the presence of an active circulation and an inflammatory exudate. It became slower and sometimes ceased in the chamber areas which became stable and were protected from movement and irritation, even in the

17. Kvale, W. F.; Smith, L. A., and Allen, E. V.: Speed of Blood Flow in the Arteries and in the Veins of Man, Arch. Surg. **40**:344 (Feb.) 1940.

18. Matthes, K.; Gross, F., and Goepfert, H.: Untersuchungen über die Form des peripheren Pulses beim Menschen, Arch. f. d. ges. Physiol. **242**:437, 1939.

19. Clark, E. R., and Clark, E. L.: Microscopic Observations on Growth of Blood Capillaries in Living Mammal, Am. J. Anat. **64**:251 (March) 1939.

presence of sufficient space for further extension. The same growth conditions which favored the formation of new blood vessels also stimulated the growth of other tissues in the same region.

The character of the cutaneous capillary structure of 1,100 schizophrenic patients was studied by Olkon [20] and compared with that of normal persons. In cases of schizophrenia the cutaneous capillaries showed striking deviations, consisting of reduction in number, few comma shapes, a paler color, lack of uniformity in size and a variety of bizarre shapes—spiral, crescent, hairpin-like and stellate forms and dilated, ameboid forms with pseudopodia. Moreover, the flow through the capillaries was seldom uniform; at times it was more rapid and at times slower than normal; at other times the contractions and dilatations were remarkably irregular. Another striking feature was the frequent occurrence of capillary hemorrhage among excited schizophrenic patients. In cases of hebephrenia of long standing, sparseness of capillaries was the most marked feature, aside from the bizarre shapes already mentioned. Schizophrenic patients showed these changes, whereas normal persons of similar age did not. From these observations the author expressed the belief that since in organic and vegetative derangements there are definite disturbances in the capillaries, their presence in these patients may be corroborative evidence of the increasingly accepted theory that schizophrenia is a vegetative and metabolic disorder.

Eichna and Bordley [21] reviewed studies on capillary blood pressure and concluded that the direct microinjection method of Landis was more accurate than the indirect pressure capsule method of Danzer and Hooker. Comparisons were made at normal and at elevated levels of venous pressure. A critical test was used to evaluate the reliability of the two methods. In this test a pneumatic cuff, encircling the upper portion of the arm, was inflated to pressures below diastolic arterial pressure. The venous pressure in the hand rose to and above the cuff pressure. The extent of this rise was found to be influenced by the difference between the level in the cuff and that in the hand. The capillary blood pressure in the nail fold, recorded by the direct method, was found always to exceed the venous pressure in the hand. This phenomenon could not be demonstrated with the indirect method, as no correlation between capillary and cuff pressure was obtained. The authors thus concluded that of the two methods the direct one afforded an accurate measurement of the capillary blood pressure.

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20. Olkon, D. M.: Capillary Structure in Patients with Schizophrenia, Arch. Neurol. & Psychiat. **42**:652 (Oct.) 1939.

21. Eichna, L. W., and Bordley, J., III: Capillary Blood Pressure in Man: Comparison of Direct and Indirect Methods of Measurement, J. Clin. Investigation **18**:695 (Nov.) 1939.

In 26 of 145 patients, apparently free from circulatory disorders, Naumann [22] found the pressure in the dorsalis pedis artery to be lower than that in the radial artery. In all the other patients the reverse was observed to be true.

Oscillometry.—Atlas [23] found the practical application of the oscillometer to be disappointing because of the confusing results often obtained. Readings differed with the same person at morning and at night. Slender persons gave different readings than robut ones. On the premise that peripheral arteriosclerosis involves the lower extremities to a much greater extent than it does the upper, oscillometric readings at any given level in the lower extremities should, as the disease progresses, decrease proportionately more than those at any given level in the upper extremities. Oscillometric readings were thus taken at a given level in both the upper and the lower extremities. With the reading obtained at the supramalleolar level as the numerator and that at the distal third of the forearm as the denominator, a ratio was established which in 86 patients free from vascular diseases was found to be between 1 and 2. In no case was the ratio less than 1. In a group of 30 ambulatory patients with signs and symptoms of peripheral arteriosclerosis this ratio was found to be less than 1. In none of the latter group could pulsations be felt. This test will thus enable the examiner to demonstrate in a roughly quantitative way decreased arterial pulsations in the lower part of the leg.

Arteriography.—Dimtza and Jaeger [24] listed the usual indications for arteriography, including its usefulness in visualizing the vessels prior to amputation and in determining the degree of collateral circulation. The authors also employed this method of vascular study to differentiate organic lesions from merely vasoneurotic symptom complexes when the symptoms were doubtful. Of particular value was its use in post-traumatic circulatory disturbances, especially when there was a question of malingering. In some cases the injection of the contrast medium had a definite therapeutic effect, an observation which had previously been noted. In 7 cases (a total of 70) the material was injected periarterially, but no untoward effects were noted, other than nausea in 1 and fever in 2 cases.

Tissue Pressure.—Mayerson and Burch [25] studied the effect of posture on venous and tissue pressures in patients subject to syncope

22. Naumann, M.: Der Blutdruck in der Arteria dorsalis pedis in der Norm und bei Kreislaufstörungen, Ztschr. f. Kreislaufforsch. **31**:513 (July 15) 1939.

23. Atlas, L. N.: Oscillometry in Diagnosis of Arteriosclerosis of the Lower Extremities, Arch. Int. Med. **63**:1158 (June) 1939.

24. Dimtza, A., and Jaeger, W.: Ueber die Indikation der Arteriographie, Fortschr. a. d. Geb. d. Röntgenstrahlen **58**:40 (July) 1938.

25. Mayerson, H. S., and Burch, G. E.: Relationships of Tissue (Subcutaneous and Intramuscular) and Venous Pressures to Syncope Induced in Man by Gravity, Am. J. Physiol. **128**:258 (Jan.) 1940.

on changes in position. They found that the venous (foot) and intramuscular (gastrocnemius) pressures in the resting horizontal position were lower in persons who were liable to postural syncope than in those who were not. Tilting the subjects from the horizontal to the upright (75 degree) position was followed by immediate and simultaneous rises in venous, subcutaneous and intramuscular pressures. Subjects who did not have syncope showed a secondary, usually more marked, increase in intramuscular pressure during the upright period, a change which was absent in those who showed circulatory embarrassment. Intramuscular pressure was affected by the tonus of the muscle fibers, as well as by the amount of intravascular and extravascular fluid present. When the tonus was low the value for intramuscular pressure tended to approach that for subcutaneous pressure.

Effect of Drugs.—During the past few years articles have appeared demonstrating differences between the vessels of the skin and those of deeper structures. The responses of these types of vessels to various therapeutic procedures were in many cases not necessarily parallel. Such differences were demonstrated by Friedlander, Bierman and Silbert,[26] who recorded the changes in temperature in the muscles of the calf and in the skin of the feet following the intravenous administration of typhoid vaccine. The temperatures employed ranged from 99 to 101 F., those frequently used therapeutically. Within from sixty to ninety minutes after the injection, both the rectal and the cutaneous temperature increased, but a gradual fall in the temperature of the calf muscle was noted. In many of the cases the cutaneous temperature dropped at the onset of the chill but rose above the initial level after the tremors subsided. Muscle temperature was not affected by either chills or tremors. The authors concluded from their data that an elevation of systemic temperature to 101 F. is associated with an increase in the circulation of the skin of the feet and a decrease in the circulation of the calf muscles. They expressed the belief that this type of therapy might be beneficial for ulcers, but that its use for relief of intermittent claudication appeared to have no physiologic basis. In a later paper [27] they again demonstrated this phenomenon by studying the effect on the temperature of the skin and toes and the muscles of the calf of seven methods employed to alter the circulation in the lower extremities. In addition to the intravenous injection of typhoid vaccine, these methods consisted of: (1) lumbar paravertebral injections of alcohol; (2) spinal anesthesia; (3) intravenous injections of a hyper-

26. Friedlander, M.; Bierman, W., and Silbert, S.: Temperature Changes in Skin and Muscle of Lower Extremities Following Intravenous Injections of Typhoid Vaccine, Proc. Soc. Exper. Biol. & Med. **41**:221 (May) 1939.

27. Friedlander, M.; Silbert, S., and Bierman, W.: Regulation of Circulation in the Skin and Muscles of the Lower Extremities, Am. J. M. Sc. **199**:657 (May) 1940.

tonic solution of sodium chloride; (4) intravenous injections of physiologic solution of sodium chloride; (5) intravenous injection of epinephine, and (6) immersion of the forearms in hot water. With one exception, all the methods employed produced increase in the temperature of the skin, with reverse or no changes in the muscles. Hypertonic solution of sodium chloride was unique in its ability to increase the circulation in both the skin and the muscles. Although the temperature of the muscles did increase, the amount was slight, being approximately 25 per cent of that in the skin. This should be considered a small rise when one considers the mild dilatation produced by hypertonic solution of sodium chloride alone. A similar rise in temperature of the muscles followed the administration of epinephrine, but the cutaneous temperature was lowered. Sympathetic paralysis failed to increase the circulation of the muscles; thus, little physiologic basis was furnished for ganglionectomy in the treatment of intermittent claudication. The same might be said for all the other methods, with the possible exception of injection of a hypertonic solution of sodium chloride and of epinephrine.

Haury [28] was able to demonstrate vasodilatation in the extremities of 7 patients following the intravenous administration of magnesium sulfate. A glass oncometer was used to determine the presence of vasodilatation. The usual dose was 20 cc. of a 10 per cent solution, and dilatation persisted for ten to thirty minutes. In 1 case of Raynaud's disease the usual intravenous injection was supplemented by intramuscular injection of 2 cc. of a 50 per cent solution of magnesium sulfate, and the patient reported relief of symptoms for twenty-four hours. As symptoms in Raynaud's disease occur in episodes, this result means little. It has been the experience of this author that this salt should be used with great caution, as serious consequences are not uncommon.

The action of nicotinic acid on the peripheral circulation was again studied by Popkin.[29] Fifteen adults were given 30 to 120 mg. of nicotinic acid by mouth. As had previously been noted, the majority of patients had transitory flushing of the skin, tingling, itching and sensation of heat, regardless of the condition of the subject or the size of the dose. Changes in the surface temperature of the face, fingers and toes were variable and unpredictable. The amplitude of the oscillometric tracings was diminished, varying directly with the quantity administered. The authors agreed that the effects of nicotinic acid were similar to those produced by histamine and of little value in the therapy of peripheral vascular diseases.

28. Haury, V. G.: The Effect of Intravenous Injections of Magnesium Sulfate on the Volume of the Extremities, J. Lab. & Clin. Med. **24**:951 (June) 1939.

29. Popkin, R. J.: Nicotinic Acid: Its Action on the Peripheral Vascular System, Am. Heart J. **18**:697 (Dec.) 1939.

Theis and Freeland [30] studied the effect of intravenous administration of sodium tetrathionate and sodium thiosulfate on normal persons and patients with peripheral vascular diseases, particularly those with thromboangiitis obliterans. In many cases there were increase in peripheral temperature, decrease in pulse rate and reduction in blood pressure. Changes in oxygen capacity and oxygen saturation of the arterial and venous blood were noted. Changes in oxygen saturation, however, were not as marked in patients with thromboangiitis obliterans as they were in the control group or in patients with other types of circulatory disease. The effects of these two drugs were noted to have an effect opposite that of tobacco. They were therefore concluded to be of value in treatment of thromboangiitis obliterans, but no mention was made of the therapeutic results.

Cohen and Rosen [31] demonstrated dilatation of the capillaries and arterioles of the web of the frog's foot after the application of various ointments containing acetylbetamethylcholine chloride. With ointments containing histamine hydrochloride dilatation was noted only in the capillaries, with general constriction of the arterioles. Clinically these ointments produced a satisfactory erythema in all patients to whom they were applied. They were found to be more effective when used in compound ointment of menthol base, and heat was found to enhance their action. Beneficial results were obtained in patients with arthritic pains presumably secondary to coexisting circulatory disturbances.

Reynolds and Foster [32] observed the effect of estrogenic substance on the blood vessels of the rabbit's ear. Direct visualization and temperature studies were made. The authors concluded that this hormone caused dilatation of the minute vessels, not, however of maximal degree. They noted that the rate of blood flow through the ear varied, not with the degree of vasodilatation brought about by the estrogen but with the requirements for heat loss which dilatation of the smaller vessels imposed in the regulation of normal body temperature under various experimental conditions.

A clinical study followed in which the authors [33] noted the effects of estrogen on the peripheral circulation by observing the changes in

30. Theis, F. V., and Freeland, M. R.: Thromboangiitis Obliterans: Treatment with Sodium Tetrathionate and Sodium Thiosulfate, Arch. Surg. **40**:190 (Feb.) 1940.

31. Cohen, A., and Rosen, H.: Mecholyl and Histamine Effects on Peripheral Circulation and Relief of Arthritic Pain, Arch. Phys. Therapy **21**:12 (Jan.) 1940.

32. Reynolds, S. R. M., and Foster, F. I.: Peripheral Vascular Action of Estrogen, Observed in the Ear of the Rabbit, J. Pharmacol. & Exper. Therap. **68**:173 (Jan.) 1940.

33. Reynolds, S. R. M., and Foster, F. I.: Peripheral Vascular Action of Estrogen in the Human Male, J. Clin. Investigation **18**:649 (Nov.) 1939.

cutaneous temperature and finger volume following the injection of estrogen in 20 normal men. Observations on the effect of single injections of the estrogen were made on all subjects, with the exception of 3 who received two injections and 1 who received nine injections. Approximately two thirds of the patients showed an effect involving an increase in finger volume, which commenced a few minutes after the injection and continued from thirty to sixty minutes. The average increase in finger volume was 4.6 per cent. No change in cutaneous temperature was observed. Injection of an unknown substance, corn oil, as a vehicle had no such effect on finger volume in these subjects. The character of the response, with other established facts regarding the vascular effects of estrogen, indicated that it depended on dilatation of the small vessels in the skin beyond the arterioles. There was no measurable increase in the rate of blood flow in the skin. The failure of estrogen to bring about dilatation of the cutaneous vessels in some subjects was unexplained.

Thomas [34] repeated the existing experimental studies on the effect of theelin and testosterone propionate on the incidence of gangrene of the rat's tail induced by ergotamine tartrate. He found that neither substance affected or altered the gangrene of either male or female rats.

For determining the effect of massive doses of insulin on the peripheral circulation of 7 patients with schizophrenia, Abramson and his colleagues [35] used the plethysmographic method. They stated that a marked increase in blood flow was usually observed in the hand, forearm and leg at the height of the hypoglycemic response. When the hypoglycemia was terminated by the administration of carbohydrate, a rapid decrease in blood flow to below the control level usually occurred, especially in the hand. When dextrose was given without the previous injection of insulin, this effect on the blood flow was not apparent.

During the hypoglycemic state, when the blood flow to the arm was increased about two and three-tenths times, the blood from the forearm showed a significant decrease in arteriovenous differences for both oxygen and carbon dioxide. From chemical changes of the same magnitude in both blood from the brain and that from the arm, previous workers have concluded that there is no significant change in cerebral blood flow during the hypoglycemic state. From these studies, however, one notes the necessity for obtaining simultaneous changes in the blood flow and in the chemical constituents for proper evaluation of the data.

34. Thomas, R. M.: Sex Hormone Therapy in Experimental Peripheral Gangrene, Yale J. Biol. & Med. **12**:415 (March) 1940.

35. Abramson, D. I.; Schkloven, N.; Margolis, M. N., and Mirsky, I. A.: Influence of Massive Doses of Insulin on Peripheral Blood Flow in Man, Am. J. Physiol. **128**:124 (Dec.) 1939.

DeBakey, Burch and Ochsner [36] studied the effect on the peripheral pulse volume of ligation of a vein and chemical irritation of a venous segment. This study was made on the hindfeet of 12 dogs, and the measurements were determined with the plethysmograph. After the ligation of the main veins of the hindleg the volume of pulsation diminished markedly (52.5 per cent). It was also observed that the venous pressure increased from a mean value of 7.7 cm. of water before ligation to one of 97.0 cm. after ligation. This effect was not influenced by the presence or the absence of the sympathetic ganglions and the intervening chain.

When a segment of the main vein was chemically irritated by injection either into the lumen or in the perivascular tissues, a marked diminution of the peripheral pulse volume (51.6 per cent) occurred. In these experiments the interruption of nerve pathways either by local infiltration of procaine hydrochloride at the site of the irritation or by resection of the lumbar sympathetic ganglions and chain abolished this effect. This suggested that the decrease in the volume of pulsations following chemical phlebitis or periphlebitis was due to vasoconstrictor impulses initiated locally by the chemical irritant and coursing through the sympathetic ganglions to reach the terminal arterial vessels of the extremity.

Fatherree, Adson and Allen,[37] in continuing their work on the effect of epinephrine on smooth muscle after sympathectomy, concluded that both preganglionic and postganglionic section for Raynaud's disease of the hands caused increased sensitivity of the arteries to epinephrine, but that the degree of increased sensitivity was the same in the two instances. This is contrary to previously reviewed articles, in which it was maintained that preganglionic section for Raynaud's disease produced better clinical results than ganglionectomy, because the former operation did not greatly increase sensitivity to epinephrine while the latter did. After sympathectomy for Raynaud's disease of the lower extremities the authors found little increase in sensitivity of the digital arterioles to epinephrine. Even though this was in keeping with clinical results, Fatherree and his colleagues were unable satisfactorily to explain the occasional unfavorable result in cases of Raynaud's disease of the hands on the basis of sensitivity of the arterioles to epinephrine.

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36. DeBakey, M.; Burch, G. E., and Ochsner, A.: Effect of Chemical Irritation of a Venous Segment on Peripheral Pulse Volume, Proc. Soc. Exper. Biol. & Med. **41**:585 (June) 1939.

37. Fatherree, T. J.; Adson, A. W., and Allen, E. V.: The Vasoconstrictor Action of Epinephrine on the Digital Arterioles of Man Before and After Sympathectomy, Surgery **7**:75 (Jan.) 1940.

Steck and Gellhorn [38] studied the effect of the inhalation of oxygen-deficient gas mixtures and of carbon dioxide in air on the peripheral blood flow in the hand of sympathectomized patients. Previously reviewed articles have shown that carbon dioxide regularly reduces the blood flow in normal persons. This reaction did not occur after sympathectomy. The flow remained essentially unchanged with low concentrations of carbon dioxide, but with higher concentrations the flow was increased. It was the opinion expressed by the authors that this increased flow was due to the increased blood pressure and dilating action of carbon dioxide on the peripheral blood vessels, which is unopposed by the normally present and increased sympathetic impulses originating in the vasomotor center. They were unable to determine the presence or absence of sympathetic impulses by this method.

Zothe [39] suggested the therapeutic use of strophanthin in cases of peripheral vascular disturbances. When this drug was given intravenously in therapeutic doses improvement of the depressed muscular contraction occurred. This beneficial effect was attributed to better utilization of oxygen by the tissue rather than to increased blood flow.

Effect of Tobacco.—Abramson, Zazeela and Oppenheimer [40] continued their plethysmographic studies of blood flow in the hand, forearm and foot. These investigations showed that smoking caused a decrease in peripheral blood flow, which took place, however, only in the blood vessels of the skin, and not in those of voluntary muscle. This constrictor response observed in the cutaneous vessels of the hand cannot therefore be considered as typical of reactions of blood vessels elsewhere in the body. These findings again emphasize the independent action of the arteries of the skin and of the muscles.

The relationship between tobacco and peripheral vasospasm was again studied by Moyer and Maddock.[41] Twenty subjects were observed during smoking. In all cases a progressive decrease in cutaneous temperature was noted. The period of recovery following cessation of smoking was variable; in no case was it less than five or more than seventy minutes. It was found that the temperature of the fingers

38. Steck, I. E., and Gellhorn, E.: The Effect of Carbon Dioxide Inhalation on the Peripheral Blood Flow in the Normal and in the Sympathectomized Patient, Am. Heart J. **18**:206 (Aug.) 1939.

39. Zothe, H.: Untersuchungen über die Wirkung des Strophanthins bei peripheren Durchblutungsstörungen, Ztschr. f. Kreislaufforsch. **30**:889 (Dec.) 1938.

40. Abramson, D. I.; Zazeela, H., and Oppenheimer, B. S.: Plethysmographic Studies of Peripheral Blood Flow in Man: III. Effect of Smoking upon the Vascular Beds in the Hand, Forearm and Foot, Am. Heart J. **18**:290 (Sept.) 1939.

41. Moyer, C. A., and Maddock, W. G.: Peripheral Vasospasm from Tobacco, Arch. Surg. **40**:277 (Feb.) 1940.

returned to normal more rapidly than did that of the toes, the difference in the time being as much as three minutes in some cases. After a second cigaret the changes described again occurred.

The possibility that the alteration in rate, rhythm and depth of breathing incident to smoking might have produced these changes was discarded, as no changes occurred when the subjects were asked to simulate smoking by puffing on a small paper tube or an empty pipe. The possibility that they were due to carbon monoxide was found not to hold when no vascular response could be elicited with cubeb cigarets. Cardiovascular changes occurred to a lesser degree when the smoke was filtered through two bottles or through a layer of cotton impregnated with ferric chloride. Some of the subjects studied had far advanced occlusive vascular disease, but vasoconstriction could still be demonstrated after smoking.

As a direct proof that nicotine was the principal activator of this vasomotor response, 0.1 mg. of the drug injected intravenously produced marked peripheral vasoconstriction. No response was obtained when nicotine was given by mouth, even though 1 mg. was given every ten minutes for six doses. Apparently an insufficient quantity was absorbed into the blood stream to produce cardiovascular response.

In spite of this evidence, Mulinos and Shulman [42] asserted that the deep breathing usually associated with smoking is a factor in vasoconstriction. They used five methods to analyze the response of blood vessels to smoking and deep breathing. The rate of blood flow was studied with the pressure plethysmograph of Hewlett and Van Zwaluwenburg. Changes in volume were measured with a single plethysmograph, and a skin calorimeter was used as an indicator of the available heat in the skin. The remaining two methods consisted of thermopile studies of cutaneous temperature and capillary microscopy. Deep breathing alone could account for the decreased rate of blood flow, loss of hand volume and visible capillary changes equally as well as could smoking. In studies of cutaneous temperature both deep breathing alone and smoking decreased the temperature, but in the majority of cases a greater fall occurred after smoking. The subjects who did not inhale cigaret smoke showed a greater vascular response of the hand from ten deep breaths than from the puffing and a lesser response than did those who inhaled the cigaret smoke. Inhaling the smoke from denicotinized cigarets resulted in as great vasoconstriction as inhaling the smoke from a standard brand cigaret, and occasionally the response was greater. Although these findings of Mulinos and Shulman are not compatible with those reported in the majority of articles, it is interesting

42. Mulinos, M. G., and Shulman, I.: The Effects of Cigarette Smoking and Deep Breathing on the Peripheral Vascular System, Am. J. M. Sc. **199**:708 (May) 1940.

to note the response of deep breathing alone on the peripheral vascular system. One wonders if these authors request their patients to refrain from deep breathing because of its vasoconstricting effect.

Harkavy [43] summarized all of his work on cutaneous reactions to tobacco and answered the many criticisms. The incidence of cutaneous reactions to tobacco was studied in (1) 400 normal smokers, both male and female; (2) 126 women nonsmokers; (3) 319 control smokers, consisting of 47 normal persons and 292 adults patients suffering from various ailments; (4) 140 patients with thromboangiitis obliterans; (5) 31 patients with peripheral vascular disease associated with arteriosclerosis, and (6) 100 patients with coronary disease and angina pectoris. These studies indicated that positive cutaneous reactions to tobacco (prepared according to a method that the author described) represent a true immunologic response. This was demonstrated by (1) the presence of tobacco reagins in patients reacting positively, (2) the specific absorption of these reagins by corresponding tobacco allergens in patients with multiple sensitization and (3) the induction of a characteristic local eosinophilic reaction in the immediate urticarial response of patients with thromboangiitis obliterans, disease of the coronary arteries and migrating phlebitis tested intradermally with tobacco. This was further attested experimentally, in that 33 per cent of male rats given daily intraperitoneal injections of the same tobaccos employed in testing the patients had gangrene of the toes. These animals were shown to be sensitized to tobacco by the Schultz-Dale technic. Of the 140 patients with thromboangiitis obliterans tested with ragweed and timothy pollen, horse dander and tobacco, 68 per cent gave positive reactions of 1 plus and over to tobacco alone, and 44 per cent of these had reagins for tobacco. An additional 10 per cent gave plus-minus reactions, making a total of 78 per cent, the patients with thromboangiitis obliterans reacting to tobacco only. This is in contrast to the 9 per cent of 400 normal control smokers who gave reactions to tobacco only. Twelve patients with thromboangiitis obliterans tested with nicotine tartrate in 1:10,000 and 1:5,000 concentrations gave completely negative reactions. Of the 100 patients with disease of the coronary arteries and angina pectoris, 44 per cent reacted to tobacco and 10 of 14 had reagins to tobacco. Harkavy inferred from these observations that tobacco allergy plays an important part in certain forms of vascular disease as well as in symptoms referable to other systems, such as the respiratory, the gastrointestinal and the cutaneous. The positive reactions assume etiologic significance, since they can be correlated with the fact that in the patients studied, particularly those with thromboangiitis obliterans or angina pectoris, with or without disease of the coronary

43. Harkavy, J.: Tobacco Skin Reactions and Their Clinical Significance, J. Invest. Dermat. **2**:257 (Oct.) 1939.

arteries, resumption of smoking called forth an exacerbation of all symptoms. Although it has been impossible to adduce any demonstrable proof of sensitization to nicotine as such, the question of hypersensitiveness to its alkaloid on theoretic grounds cannot be dismissed completely. Sensitiveness to drugs and chemicals may exist irrespective of cutaneous reactions. Aside from the possible sensitizing effect of nicotine, the pharmacologic action of the drug in all probability plays an accessory part through its constrictive influence on blood vessels, with consequent diminution in blood flow in the tissues involved. Such a result, common in all smokers, is, however, transitory in normal persons. In itself the drug evokes no notable symptoms, but it may become of utmost importance in the evolution of pathologic tissue changes in persons allergic to tobacco. In the latter, hypersensitiveness to tobacco may possibly intensify the pharmacologic action of nicotine. The immunologic and clinical evidence presented suggests that tobacco has an inciting role in thromboangiitis obliterans and in certain types of involvement of the coronary arteries.

Silbert [44] reported a case of angioneurotic edema in a 44 year old man who had thromboangiitis obliterans. He was a heavy smoker, and cutaneous tests revealed him to be markedly sensitive to tobacco. With cessation of the use of tobacco he had no attacks of angioneurotic edema and the peripheral symptoms disappeared. This case is of interest because it lends support to Harkavy's work.

Cases of acute and chronic nicotine poisoning in 24 men between the ages of 17 and 53 were reported by Weicker.[45] These men smoked between fifteen and fifty cigarets daily. Most of the patients had disease of the coronary arteries in the form of angina pectoris or cardiac infarcts. Thromboangiitis was observed in 4 men. In 2 of these, nicotine was the only demonstrable external factor capable of impairing the peripheral circulation, and in the other 2 exposure to cold and dampness may have played a part.

ARTERIOSCLEROSIS

Wilder [46] compared his views on the relation of diabetes to arteriosclerosis with those of other authors. From a study of necropsy material he concluded that sclerotic lesions of the arterioles and finer arteries do not occur with greater frequency or greater intensity in cases of diabetes than in those of other diseases, that the frequency of sclerosis of the longer arteries also was not unusual in cases of diabetes, but that the intensity of the process and the incidence of severe grades

44. Silbert, S.: Angioneurotic Edema Due to Tobacco Sensitivity and Thrombo-Angiitis Obliterans in the Same Patient, J. A. M. A. **114**:1442 (April 13) 1940.

45. Weicker, B.: Kreislaufschäden und Nicotin, Deutsches Arch. f. klin. Med. **185**:393, 1940.

46. Wilder, R. M.: Diabetic Arteriosclerosis, Internat. Clin. **2**:13 (June) 1939.

of atheromatosis and of occlusion of the lumen of the arteries of the heart and legs were significantly greater in persons with diabetes than they were in persons who were not diabetic. Women with diabetes seemed to be much more susceptible to severe grades of occlusive lesions than other women, an observation for which no explanation was apparent. Although other authors have shown that the long duration of diabetes is attended with more progression of atherosclerosis in the heart and legs than can be attributed simply to aging, Wilder expressed the belief that there is no correlation between the severity of the diabetes and that of the atherosclerosis. The contrary was also shown to be true, as many patients with diabetes of long duration remain free from clinically detectable evidence of arteriosclerosis and at necropsy present no greater degree of atheroma or other disease of the arteries than is commensurate with the degree of physiologic senile arteriosclerosis to be expected in persons of their age.

The observations of Wilder are not entirely in keeping with those of Bowen, Regan and Koenig.[47] They studied the vascular status of 52 diabetic patients who had been under observation for a period of ten to thirteen years. The patients were divided into three groups: group 1, those who had excellent or good care throughout most of their diabetic life; group 2, those who were regarded as uncooperative, and group 3, those whose diabetes had not been controlled during the period before insulin treatment, with resulting undernourishment from a low caloric diet or very severe diabetes, but whose disease had been well controlled since insulin treatment was begun. Blood pressure studies revealed that there was no correlation between the height of the blood pressure and the impairment of the circulation of the lower extremities.

The authors concluded from their observations that atherosclerosis of the lower extremities could be prevented or delayed by controlling the diabetes continuously, provided the control was started early enough after the inception of the disease. Atherosclerosis of the lower extremities did not develop in persons whose diabetes was controlled, even though the diet was moderately high in fat. An increase in body weight appeared to favor atherosclerosis of the lower extremities, but since in most instances this was associated with poor control of the diabetes it was impossible to appraise the effect of stoutness. In a small series of patients no relationship existed between the degree of atherosclerosis of the lower extremities and the complicating coronary occlusion. Coronary occlusion seemed to be favored by stoutness. Eleven of the patients showed lack of parallelism between calcification of the arteries of the lower extremities and the state of the circulation. The authors

47. Bowen, B. D.; Regan, J. S., and Koenig, E. C.: The Development of Arteriosclerosis in the Diabetic, Based on the Study of a Group of Patients During Ten to Thirteen Years, Ann. Int. Med. **12**:1996 (June) 1939.

expressed the belief, however, that the demonstration of calcification of the arteries must be regarded as accessory evidence of atherosclerosis, which may be assumed if a patient has had uncontrolled diabetes for some time. Five of the patients had had calcification of the arteries of the lower extremities for thirteen years.

Barker [48] studied the plasma lipoids in a series of 73 patients with arteriosclerosis obliterans without diabetes mellitus and compared them with a control series of 200 subjects of various ages who were considered normal. The ranges for the total lipoids and the various lipoid fractions were essentially the same in the two groups. These lipoid fractions consisted of cholesterol, cholesterol esters, phospholipids and fatty acids. The mean values for all the fractions and for the total lipoids were, on the other hand, definitely and significantly higher in patients with arteriosclerosis than in the control group. Barker expressed the opinion that since the plasma lipoids have been shown to be essentially normal in cases of thromboangiitis obliterans, these high values for plasma cholesterol and total lipoids might be of a diagnostic aid in cases in which differentiation between the two entities is difficult. Diets low in animal fats were given 8 patients with arteriosclerosis obliterans having comparatively high lipoid levels, with consequent lowering of the level in 4 of them. Barker has now observed 3 cases in which arteriosclerosis obliterans, xanthoma tuberosum and marked lipema occurred together. A detailed description of 2 of these cases was reported previously by the same author.[49]

The functional state of a vessel wall was found to influence the incidence and severity of experimental arteriosclerosis. Harrison [50] performed unilateral lumbar sympathectomy on a series of rabbits, which were subsequently fed large doses of cholesterol in oil. A control group received the same diet, but no operative intervention. Studies of the cutaneous temperatures were constantly employed during the experiment to make sure of the presence of dilatation in the sympathectomized extremity. At the completion of the experiments, Harrison found the vascular lesions in the extremity on the side of operation to be more severe than those of the opposite extremity. In the control animals there was no significant difference between the two extremities. Chemical estimations of the amount of cholesterol deposited in the vessels

48. Barker, N. W.: The Plasma Lipoids in Arteriosclerosis Obliterans, Ann. Int. Med. **13**:685 (Oct.) 1939.

49. Barker, N. W.: Occlusive Arterial Disease of the Lower Extremities Associated with Lipemia and Xanthoma Tuberosum, Ann. Int. Med. **12**:1891 (May) 1939.

50. Harrison, C. V.: Effect of Sympathectomy on Development of Experimental Arterial Disease, J. Path. & Bact. **48**:353 (March) 1939.

confirmed his observations. Harrison thus concluded that sympathetic paralysis enhances the effect of cholesterol in producing experimental arteriosclerosis.

Temporal Arteritis.—Two cases of temporal arteritis were reported by Dick and Freeman,[51] making a total of 13 such cases now recorded in the literature. In all of these cases the authors have described a similar syndrome. The disease occurs chiefly in old people, the average age being 67. Weakness and general malaise prior to and during the local involvement of the arteries about the head were noted. The period of prodromal symptoms varied from two weeks to eight months, although it was not always clear whether the contiguous signs and symptoms were related to this disease. All of the patients had headaches, which were often throbbing and associated with tenderness of the scalp and painful mastication. The swelling and redness of the periarterial tissues usually followed the onset of the headache. Fever was invariably present. The disease usually ran a self-limiting course, lasting several months. Although temporal arteritis has some similarity to periarteritis nodosa, thromboangiitis obliterans and rheumatic arteries, its cause remains obscure. The pathologic picture is that of simple arteritis; however, Dick and Freeman noted giant cells in the inflammatory process. Because of the age incidence, the syndrome is probably related to degenerative vascular changes with a superimposed infection.

ANEURYSM

The absence of pulsations in the radial and carotid arteries was noted by Maurer [52] in 2 cases of aneurysm of the aortic arch.

Yater [53] reported 4 cases of ruptured popliteal aneurysms following trivial or unnoticed trauma. It was interesting to note that the pathologic study in all these cases revealed severe degenerative changes of a nonspecific nature, whereas all the patients had syphilis.

THROMBOANGIITIS OBLITERANS

An excellent article on the diagnosis and management of chronic obliterative vascular disease was submitted by McKittrick.[54] Although most of the material in his article has been mentioned in former reviews,

51. Dick, G. F., and Freeman, G.: Temporal Arteritis, J. A. M. A. **114**:645 (Feb. 24) 1940.

52. Maurer, E.: Absence of Pulse in the Vessels of the Upper Extremities and Neck in Aneurysm of the Aortic Arch, Am. Heart J. **17**:716 (June) 1939.

53. Yater, W. M.: Ruptured Popliteal Aneurysm: Report of Four Cases, Am. Heart J. **18**:471 (Oct.) 1939.

54. McKittrick, L. S.: The Diagnosis and Management of Chronic Obliterative Vascular Disease, J. A. M. A. **113**:1223 (Sept. 23) 1939.

one observation is worthy of note. In the differential diagnosis of thromboangiitis obliterans and arteriosclerosis the age of the patient and the roentgenographic evidence of calcification in the vessels play a major role in diagnosis. A definite diagnosis of thromboangiitis obliterans can usually be made in a man 40 years of age or younger, with symptoms of years' rather than of months' duration, without the roentgenographic evidence of calcification and with a normal sugar content of the blood. A probable diagnosis can be made in a man between the ages of 40 and 55 with symptoms of more than one year's duration and with slight or no evidence of calcification, particularly if there is evidence of involvement of an upper extremity. A diagnosis of this disease is rarely made in a patient over 55 years of age, with or without roentgen evidence of calcification and with a history of less than one year's duration. McKittrick stated that he would be unwilling to make a diagnosis of thromboangiitis obliterans in a woman over 40. The diagnosis of arteriosclerosis was usually made in the older age groups. In 30 per cent of 66 proved cases roentgenographic evidence of calcification was lacking. A diagnosis of arteriosclerotic obliterative disease may be made with reasonable certainty in a patient 55 years of age or over with symptoms of less than one year's duration and with roentgenographic evidence of calcification. The author expressed the belief that it is impossible to make a positive diagnosis in a man between the ages of 40 and 55 with symptoms of approximately a year's duration and with little or no evidence of calcification on roentgen examination. As the combination of diabetes and thromboangiitis obliterans is rare, McKittrick stated that he feels justified in making a diagnosis of so-called diabetic gangrene in the case of any patient, male or female, with definite evidence of obliterative arterial disease associated with diabetes.

Hausner and Allen [55] commented on the generalized arterial involvement in thromboangiitis obliterans. In 5.7 per cent of a group of 500 patients who had this disease, the coronary arteries were diseased. Two per cent had clinical evidence of cerebrovascular involvement, and 3 cases had abdominal involvement. All these cases have been previously reported and included in former reviews. In 1 case the pulmonary artery and the peripheral arteries were affected. Hausner and Allen reviewed the literature and found reports of involvement of the renal, splenic, spermatic, carotid, retinal, adrenal, pancreatic, duodenal, hepatic and prostatic arteries, as well as of the aorta. They concluded that thromboangiitis may be a widespread disease, but that when the arterial lesions

55. Hausner, E., and Allen, E. V.: Generalized Arterial Involvement in Thrombo-Angiitis Obliterans Including Report of a Case of Thrombo-Angiitis Obliterans of a Pulmonary Artery, Proc. Staff Meet., Mayo Clin. **15**:7 (Jan. 3) 1940.

are outside the extremities they are almost always degenerative, in contrast to the inflammatory nature of the vascular lesions in the extremities.

Wagener [56] presented an interesting review of disease in the walls of the retinal vessels, associated with recurrent hemorrhagic extravasations into the vitreous. He stated the opinion that in a certain number of cases of this condition, particularly of the perivenous type, the disease may be due to tuberculosis; however, in a larger number in which tuberculosis cannot be demonstrated elsewhere in the body, a primary nonspecific inflammatory or degenerative lesion of the vessel wall should be suspected. This lesion, he asserted, may well be the retinal counterpart of thromboangiitis obliterans and may be confined to the retinal vessels, or at times be associated with similar lesions in other parts of the body.

RAYNAUD'S DISEASE

Leys [57] described a case of diffuse scleroderma and Raynaud's syndrome resulting from the use of the pneumatic hammer. The description of the case was too brief for confirmation, but the author expressed the opinion that injury from the pneumatic hammer was purely incidental to the other two conditions, although it might have aggravated existing conditions.

A condition resembling Raynaud's disease was described by Oberdörffer [58] in a 30 year old woman suffering from leprosy. The patient had attacks of blackness of the tips of the fingers with coldness which subsided in two weeks, leaving acroteric areas. Although few data were given to establish the diagnosis, the case is reported as one of pseudo Raynaud's disease.

PERIARTERITIS NODOSA

The majority of articles concerned with periarteritis nodosa still consist of case reports, each usually supporting one of the many etiologic theories.

Harris, Lynch and O'Hare [59] reported 6 additional cases of proved periarteritis nodosa. They noted that prior to June 1, 1938, only 101 cases had been reported in the English literature. These cases were

56. Wagener, H. P.: Thrombo-Angiitis of the Retinal Vessels, Am. J. M. Sc. **199**:296 (Feb.) 1940.

57. Leys, D.: Diffuse Scleroderma and Raynaud's Phenomenon from Use of Pneumatic Hammer, Lancet **2**:692 (Sept. 23) 1939.

58. Oberdörffer, M. J.: Pseudo-Raynaud's Disease in Leprosy, Internat. J. Leprosy **7**:395 (July-Sept.) 1939.

59. Harris, A. W.; Lynch, G. W., and O'Hare, J. P.: Periarteritis Nodosa, Arch. Int. Med. **63**:1163 (June) 1939.

studied, and the frequencies of symptoms, signs and abnormal laboratory findings were tabulated. They were unable to answer the question of causation. A history of allergy was obtained in only 15 per cent of the cases, which is not sufficient to substantiate the proposed theory of an allergic origin. The infrequency of pains in the joints and other arthritic manifestations is worthy of mention. Nothing could be added to the pathologic picture, as it appears to be well established. Although there were 26 antemortem diagnoses in the 101 cases, an analysis of the clinical symptoms and signs did not reveal a characteristic clinical pattern. The order of frequency of the more significant symptoms and signs were as follows: fever, leukocytosis, albuminuria, rapid onset, abdominal pain, edema, loss of weight, hematuria and neuritis. Of the 101 patients, 10 were reported as "recovered," indicating that the disease is not "100 per cent fatal."

Additional cases were reported by Fitz, Parks and Branch;[60] Sawyer;[61] Emerson, Schroeder and Maynard;[62] Cleland;[63] Allen;[64] Trasoff and Scarf;[65] Weir,[66] and Matras.[67] The report by the last-mentioned author is of interest in that the pathologic changes were confined to the skin.

THROMBOSIS AND EMBOLISM

Lueth[68] reported 4 cases of thrombosis of the abdominal aorta. Although this disorder is relatively infrequent, it is by no means a rare clinical entity. Diagnosis was difficult because of the variability of symptoms. Lueth stated that its recognition was dependent on the rapidity and extent of arterial closure of the aorta. The slower the

60. Fitz, R.; Parks, H., and Branch, C. F.: Periarteritis Nodosa, Arch. Int. Med. **64**:1138 (Dec.) 1939.

61. Sawyer, C. F.: Necrotizing Arteritis (Periarteritis Nodosa), Surgery **6**: 717 (Nov.) 1939.

62. Emerson, R. S.; Schroeder, H. A., and Maynard, E. P., Jr.: Periarteritis Nodosa: Its Clinical Recognition with Report of Illustrative Case, Brooklyn Hosp. J. **1**:107 (April) 1939.

63. Cleland, J. B.: Periarteritis Nodosa, with Report of Two New Cases, M. J. Australia **1**:846 (May 14) 1938.

64. Allen, P. D.: Periarteritis Nodosa Simulating an Acute Abdominal Condition Requiring Operation, Arch. Surg. **40**:271 (Feb.) 1940.

65. Trasoff, A., and Scarf, M.: Periarteritis Nodosa and Asthma, J. Allergy **11**:277 (March) 1940.

66. Weir, D. R.: Polyarteritis Nodosa: Report of Case, Am. J. Path. **15**: 79 (Jan.) 1939.

67. Matras, A.: Zur kutanen Form der Periarteritis Nodosa, Wien. klin. Wchnschr. **51**:991 (Sept. 16) 1938.

68. Lueth, H. C.: Thrombosis of the Abdominal Aorta: A Report of Four Cases Showing the Variability of Symptoms, Ann. Int. Med. **13**:1167 (Jan.) 1940.

formation of obstruction, the more delayed the onset of symptoms. Absence of peripheral pulsation was not necessarily diagnostic. Sharp shooting pains in the legs, abolition of femoral, popliteal or posterior tibial pulsations, and ascending gangrene of the legs were cited as supportive evidence. Coincident with the arrest of flow to the legs there were frequently symptoms resulting from ischemia of the spinal cord.

Lueth stated the opinion that the symptoms last mentioned had not received sufficient attention. The coincidence has been demonstrated repeatedly in many laboratories in a variety of animals. Anatomically it is logical, as many of the branches of the lower abdominal aorta go to the spinal cord.

Fry [69] also reported 3 cases of embolism and thrombosis of the abdominal aorta. His patients survived from one to five years after the onset of occlusive symptoms. In only 1 of the patients did gangrene develop, in spite of the high level of occlusion. Because of the slow onset the symptoms were minor, consisting of pain and, as Lueth stressed, symptoms of involvement of the cord, namely, disturbances in sensation and muscle power in the lower extremities.

Fetterman and Spitler [70] cited clinical examples of neuropathy due to defective blood supply to nerves. They expressed the opinion that involvement of the main arterial trunk to a nerve or simultaneous lesions in smaller branches (vasa nervorum) were responsible for such ischemic changes in the nerve. The literature on this subject was adequately reviewed, and cases of other authors, usually verified by pathologic studies, were discussed. Such lesions had been reported in cases of thromboangiitis obliterans, arteriosclerosis, embolism, thrombosis, syphilis and periarteritis nodosa. In the cases described by Fetterman and Spitler, the neuropathy was thought to be due to vascular complications in the vasa nervorum. As the etiologic factor was obscure and pathologic studies were not obtainable, the final solution remained a matter of individual opinion.

Wolf and Levinsohn [71] reported on an unusual arterial complication in an infant with mongolism and congenital heart disease (tetralogy of Fallot). Thrombosis involved the patent ductus arteriosus, the ascending aorta, the left common carotid artery and the left subclavian, axillary and brachial arteries.

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69. Fry, F. W.: Embolism and Thrombosis of the Abdominal Aorta, Am. Heart J. **18**:57 (July) 1939.

70. Fetterman, J. L., and Spitler, D. K.: Vascular Disorders of Peripheral Nerves, J. A. M. A. **114**:2275 (June 8) 1940.

71. Wolf, I. J., and Levinsohn, S. A.: Arterial Occlusion in the Left Upper Extremity on a Mongoloid Idiot with Congenital Heart Disease (Tetralogy of Fallot), Am. Heart J. **18**:241 (Aug.) 1939.

Gitlow and Goldmark [72] described 2 cases in which the pathologic process was characterized by generalized capillary and arteriolar thrombosis. Clinically the 2 cases varied; in the first case there was purpura with capillary thrombi, and in the second, atypical verrucous endocarditis with lupus erythematosus.

Dunphy and Whitfield [73] discussed mesenteric vascular disease on the basis of a study of 30 cases. The etiologic factors were not sufficiently obvious clinically to be considered essential in the diagnosis of this condition. In many cases pathologic changes elsewhere had rendered the patients moribund before the abdominal vascular accident occurred. The authors divided the clinical manifestations into three groups: those which result from spasm or small, nonfatal occlusions of the mesenteric arteries, so-called abdominal angina or abdominal intermittent claudication; those which follow extensive occlusion of a mesenteric artery or vein, "mesenteric vascular occlusion," and those which are a consequence of the rupture of a sclerotic artery with peritoneal hemorrhage, "intra-abdominal apoplexy." In the cases of "abdominal angina" they noted a severe, deep-seated pain in the upper part of the abdomen, usually following meals. They expressed the belief that in the absence of abnormal roentgen findings one is justified in diagnosing this pain as of vascular origin. The most significant diagnostic feature of the second type is the marked contrast between the severity of the pain and the paucity of the physical findings. The pain is severe and persists after ordinary measures have been instituted for its relief. Frequently deep abdominal tenderness, more or less generalized, with rebound tenderness, can be elicited. In later stages peritonitis may develop. The leukocyte count and pulse rate were almost invariably elevated disproportionately to the temperature. Lastly, constipation, diarrhea and a variable amount of vomiting may develop.

Crile and Newell [74] reported a case of abdominal apoplexy in which the patient, who was known to be hypertensive, had spontaneous rupture of a sclerotic visceral vessel. The hemorrhage was controlled surgically. The authors wondered why this does not occur more frequently.

Three cases of dilatation and thrombosis of the subclavian artery resulting from abnormalities of the cervical and first thoracic ribs were reported by Eden.[75] Evidence was brought forward to support the

72. Gitlow, S., and Goldmark, C.: Generalized Capillary and Arteriolar Thrombosis, Ann. Int. Med. **13**:1046 (Dec.) 1939.

73. Dunphy, J. E., and Whitfield, R. D.: Mesenteric Vascular Disease, Am. J. Surg. **57**:632 (March) 1940.

74. Crile, G., Jr., and Newell, E. T., Jr.: Abdominal Apoplexy: Spontaneous Rupture of a Visceral Vessel, J. A. M. A. **114**:1155 (March 30) 1940.

75. Eden, K. C.: The Vascular Complications of Cervical Ribs and First Thoracic Rib Abnormalities, Brit. J. Surg. **27**:111 (July) 1939.

76. Footnote omitted.

hypothesis that the vascular disease of the arm in these cases is due to damage to the wall of the subclavian artery by intermittent compression between the clavicle and the cervical or first thoracic rib. As a result, dilatation of the artery commonly occurs, with dense fibrosis around it and thrombosis. With continued trauma, a blood clot is thrown off in the form of emboli, which lodge in the vessels of the hand and arm, giving rise to progressive thrombosis and symptoms of vascular disease.

The author reviewed the literature on the vascular complications of cervical rib. There were fewer instances of vascular than of nervous complications. In the case of a vascular complication the simplest procedure is removal of the cervical rib. Division of the scalenus anterior muscle alone is insufficient to prevent further trauma. Enough of the abnormal rib is removed to allow the subclavian artery to pass freely beneath the clavicle without compression.

VEINS

Sampson, Saunders and Capp [77] studied the venous pattern of the anterior thoracic wall. The normal venous pattern was described. Prominent veins on the anterior wall of the chest were noted at all ages and were found to be extremely common after the age of 50 years. The authors expressed the opinion that most of these were produced by compression and partial obstruction of the subclavian vein between the clavicle and the first rib anterior to the scalene tubercle. Compression of the vein by tension on the clavipectoral fascia was given as an alternate explanation of the obstruction in this area. The prominent veins were thus considered to be collateral vessels, and in 1 case this was substantiated by visualization with diodrast.

In general, the authors were able, by a study of the venous pattern and the direction of blood flow, to differentiate this partial obstruction of the subclavian vein from obstruction of the innominate vein or the superior vena cava, and likewise from the distention of the veins of the chest which sometimes occurs during and after lactation.

The mechanism producing compression of the subclavian vein consisted of a projection of the first rib laterally and anteriorly against the backward and upward thrust of the clavicles. The type of person with prominent veins is, therefore, one with broad shoulders, and often a deep chest and erect posture, with shoulders held back. A high thoracic kyphosis or a slouched posture generally lowers the clavicles and moves them anteriorly, away from the ribs, preventing encroachment on the

77. Sampson, J. J.; Saunders, J. B. de C. M., and Capp, C. S.: Compression of the Subclavian Vein by the First Rib and Clavicle, with Special Reference to the Prominence of Chest Veins as a Sign of Collateral Circulation, Am. Heart J. **19**:292 (March) 1940.

subclavicular space. Thoracic scoliosis is often accompanied by asymmetric prominent veins, usually on the same side as the convexity of the spine.

Partial obstruction of the subclavican arteries produces a thrill and murmur over the arteries, and occasionally lowering of the brachial blood pressure on that side. Numbness of the arms occurred in 2 cases, and slight edema was present in 1 case.

McLaughlin and Popma [78] reported a case of intermittent obstruction of the subclavian vein appearing with exercise. During obstruction the entire extremity became swollen, blue and colder, and these changes were associated with a severe aching pain. After rest the arm returned to normal. Obstruction was demonstrated with thorium dioxide. Mechanical pressure of the first rib on the vein during activity was believed to be responsible for this syndrome, as prompt and permanent cure followed section of the scalenus anterior muscle.

Veal [79] studied the physiologic changes in an extremity produced by venous obstruction, the manner in which collateral vessels developed and the end results of such obstruction. He noted that after obstruction of the large venous trunks there was a concomitant rise in the local venous pressure with retardation of the venous flow. An associated arterial spasm was frequently noted, sufficient to produce severe pain and other signs of impaired arterial circulation. As the changes in the lymphatic and tissue fluid circulation were secondary to the increased venous pressure, the amount of edema depended on the degree of elevation of this pressure. Studies were made with venograms. Veal concluded that collateral veins developed from preexisting veins and venules. The newly developed collateral circulation was frequently found to fail because of its structural deficiencies, its superficial position and the long and devious course it often pursued. The collateral veins were in many instances inadequate because they lacked valves. If these veins were deep the squeezing effect of muscular action afforded compensation, but this could not take place if they were superficial. To promote formation of deep collateral vessels, Unna boots (occlusive dressings of zinc oxide ointment) were suggested.

Veal found that venographic studies and measurements of venous pressure were of considerable value in ascertaining the degree and extent of the venous obstruction. Repeated studies of venous pressure, made at rest and during active exercise, provided the most accurate criterion of the progress of the formation of collateral venous circulation in the extremity.

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78. McLaughlin, C. W., Jr., and Popma, A. M.: Intermittent Obstruction of the Subclavian Vein, J. A. M. A. **113**:1960 (Nov. 25) 1939.

79. Veal, J. R.: The Mode of Development of Collateral Venous Circulation in the Extremities, Am. Heart J. **19**:275 (March) 1940.

Edwards and Edwards [80] studied histologically the valves in the upper ends of varicose saphenous veins and compared them with the valves of normal veins. Most of the varices were found either to be spontaneous in origin or to follow phlebitis of the deep veins, producing a variety of pathologic changes. In the two groups the valve cusps did not show profound intrinsic lesions. The fundamental lesion was found to be a dilatation of the commissural region, that is, the portion of the wall between the attachment of the valve cusps. This was shown to give rise to evagination of the wall and separation of the cusps, producing regurgitation of blood. A growth of fibromuscular tissue on the luminal surface of the dilated commissure was noted. The cusp itself showed extrinsic changes consisting of (1) relaxation with redundancy and kinking, (2) occasionally, rolling of the free margin of the cusp, and (3) in a few cases of severe involvement, distal eversion of the cusp.

In some of the normal veins early changes similar to those present in varicose veins were seen.

The authors concluded that the regurgitation of blood in the upper saphenous vein in the usual type of varicosity was secondary to relative insufficiency of the valves, dependent on the dilatation of the venous wall. In addition, they expressed the belief that the cause of varicose veins is to be sought in the disproportion between the venous pressure and the resistance of the wall of the vein. The usual type of varicosity was therefore not caused by local infection or inflammation, thrombophlebitis or spontaneous degeneration of valves.

Biegeleisen,[81] in a study of 12 cases of so-called deep venous thrombosis with an radiopaque solution, observed no evidence of complete and lasting blockage. There was found in each case an adequate deep circulation, both from the clinical and from the roentgenographic point of view. He was unable to account for the increase in size of the involved extremity other than that due to the increase in area of the venous bed which consisted mainly of extensive collateral vascularization. As in many of these cases the condition had previously been considered "deep venous block," the injection of any of the superficial varicosities was contraindicated. Injection of these veins was in many cases found to be beneficial, and rightly so, as the studies in this series of cases clearly demonstrated patency of the deep veins. Luke [82] came to similar conclusions. He questioned the existing axiom that

80. Edwards, J. E., and Edwards, E. A.: The Saphenous Valves in Varicose Veins, Am. Heart J. **19**:338 (March) 1940.

81. Biegeleisen, H. I.: Unilateral Enlargement of Lower Extremity Accompanying Varicose Veins, with Roentgen Studies of "Deep Venous Block," Am. J. Roentgenol. **42**:683 (Nov.) 1939.

82. Luke, J. C.: The Venous Circulation in the Varicose Extremity and Its Practical Significance, Surg., Gynec. & Obst. **70**:828 (April) 1940.

varicose veins are associated with or compensatory to deep phlebitis. He presented evidence to show that the elimination of the varicosities in such cases will result in improvement of the associated symptoms of swelling, pain, eczema and ulceration.

Luke asserted that the incompetence of valves in the communicating veins had little scientific proof. He was unable to substantiate their presence by venographic studies. In his opinion, the Trendelenburg "double" reaction was more plausibly explained by incompetence of the small saphenous vein, with filling of the lower veins through the widespread anastomosis known to exist between the two saphenous veins. Clinically this was demonstrated by failure to obtain the "double" reaction when the tourniquet was applied below the knee, thus preventing the backflow of blood from the lesser saphenous vein.

Frykholm [83] studied necropsy material, comprising 24 cases of pulmonary embolism, in an attempt to learn the pathogenesis of thrombosis. Sources of beginning thrombosis were noted in the veins of four regions, namely: the musculature of the calf of the leg, the adductor musculature and the plantar and pelvic regions. An ascending thrombus seemed to pass from these regions in the direction of the blood stream, while retrograde thrombosis was rare. Early clinical diagnosis of thrombosis requires a thorough examination of these four regions. Veins with thin walls and varicose distention for a greater distance partly collapse during confinement in bed, when intima lies against intima. This occurred particularly in the musculature of the calf of the leg and the adductor muscles, which take the least part in active movements performed in bed and through which minimal amounts of blood pass. In addition there was mechanical pressure. The veins of the soles of the feet and the pelvis can also be assumed to collapse partly under certain conditions. Consequently, since normal metabolism of the intima depends on contact with the circulating blood, when two intima layers are pressed against each other, a disturbance in the nutrition of the endothelium easily occurs. This injury of the vascular endothelium was asserted to be an important primary condition in the origin of thrombosis. Substances given off by the damaged endothelium and by the thrombus promote coagulation, and the thrombus grows in the direction of the blood stream. In stagnant blood a red thrombus, and in quickly flowing blood a white thrombus, develop. The author expressed the belief that in mechanical prophylaxis against thrombosis of the lower limbs the veins of the lower extremities must, at least periodically, be sufficiently distended with blood and the circulation in the threatened region must be sufficiently rapid. Consequently, he advocated raising the head of the

83. Frykholm, R.: Pathogenesis of Venous Thrombosis and Mechanical Prophylaxis, Nord. med. (Hygiea) **4**:3534 (Dec. 2) 1939.

bed so high that the patient has the feeling of slipping down and is forced actively to exercise the muscles of the calf of the leg and the adductor group.

Barrow [84] cited an example of fatal pulmonary embolism from superficial phlebitis.

Ochsner and DeBakey [85] asserted that mechanical blockage of the venous and lymphatic systems are not of primary significance in the production of the clinical manifestations in thrombophlebitis. On the basis of recent clinical and experimental investigations they concluded that many of the symptoms and signs were due to vasospasm of the arterial and venous systems and that the vasoconstricting impulses originated in the thrombophlebitic segment. As a result of this vasospasm there occurred increased filtration pressure, relative anoxia of the capillary endothelium and diminution in the flow of lymph, all of which increased the amount of perivascular fluid, resulting in more edema. They stated that interruption of the vasoconstrictor impulses by infiltration of the sympathetic ganglions with procaine hydrochloride resulted in reestablishment of the normal exchange of intravascular and perivascular fluids.

This method was tried clinically in 15 cases involving 17 thrombophlebitic processes. Each patient was treated by procaine block of the sympathetic ganglions. Prompt and permanent relief of all the clinical manifestations resulted, in contrast to the usual production of phlegmasia alba dolens, in which there are pyrexia for from four to six weeks and the likelihood of persistent undesirable sequelae, such as edema, varicosities and ulceration. In half the cases the temperature returned to normal within forty-eight hours, and in the other half within one week. In half the cases the edema completely subsided in eight days, and in the others within twelve days. Sixty per cent of the patients were discharged from the hospital as cured within eight days after the institution of therapy.

Démarez [86] came to similar conclusions after infiltration of the lumbar sympathetic chain in 3 cases of phlebitis. The pain disappeared, the temperature decreased and edema either did not appear or did not attain the usual importance. The period of hospitalization was not as brief as that in the cases reported by Ochsner and DeBakey, although it was less than usual.

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84. Barrow, D. W.: Fatal Pulmonary Embolism from Superficial Thrombophlebitis, Ann. Surg. **110**:1118 (Dec.) 1939.

85. Ochsner, A., and DeBakey, M.: Thrombophlebitis: Role of Vasospasm in Production of Clinical Manifestations, J. A. M. A. **114**:117 (Jan. 13) 1940.

86. Démarez, R.: A propos du traitement immédiat des phlébites postopératoires en chirurgie gynécologique par infiltration du sympathique lombaire, Bull. Soc. gynéc. et d'obst. **28**:364 (May) 1939.

Former reviews have included articles on severe vasospasm complicating thrombophlebitis. Many clinical examples have been cited in which gangrene developed during the course of phlebitis. Some of these were classified under the heading of "venous gangrene." Additional cases have been reported. Gutman [87] described the case of a 21 year old girl who had postpartum gangrene, probably secondary to thrombophlebitis. Tilley [88] reported 4 cases of puerperal thrombophlebitis, in 3 of which gangrene, and in 1 a high grade vasospastic disturbance, developed.

EDEMA

Foote, Reed, Comeau and White [89] analyzed 200 unselected cases of edema of both lower extremities; the predominant causes of the edema and their frequencies were determined. Half these cases (100) were selected from the outpatient department and the other half from the wards of the hospital. In the outpatient group the causative factors occurred in the following order of frequency: varicose veins (56 cases), with obesity (31 cases) and without obesity (25 cases); obesity alone (13 cases); cardiac failure (13 cases); lymphedema (4 cases); renal disease (3 cases); nutritional factors (3 cases); cirrhosis of the liver (2 cases), and miscellaneous factors (6 cases). In the ward groups the causative factors had the following frequency: congestive heart failure (60 cases), varicose veins or obesity alone or in combination (12 cases), renal disease (7 cases), nutritional factors (7 cases), cirrhosis of the liver (7 cases), leukemia (2 cases), myxedema (2 cases) and miscellaneous factors (3 cases). This is an interesting series, particularly since cardiac failure was shown to be far less common as an etiologic factor in bilateral edema of the lower extremities than one would expect in ambulatory patients. Its predominance in ward patients is not unusual, as only those with more severe illness are admitted. From the figures just cited, it is readily seen that in all types of patients varicose veins, with or without obesity, are almost as frequent a cause of edema as cardiac failure.

Allen and Hines [90] described the clinical syndrome of lipedema. This disorder, which affects women, consists of generalized and sym-

87. Gutman, P. E.: Puerperal Gangrene of Extremities, Am. J. Obst. & Gynec. **36**:154 (July) 1938.

88. Tilley, J. H.: Gangrene of the Extremities in Puerperal Thrombophlebitis, Am. J. Obst. & Gynec. **36**:157 (July) 1938.

89. Foote, S. A., Jr.; Reed, W. C.; Comeau, W. J., and White, P. D.: The Clinical Significance of Bilateral Edema of the Lower Extremities, Am. J. M. Sc. **199**:512 (April) 1940.

90. Allen, E. V., and Hines, E. A.: Vascular Clinics: X. Lipedema of the Legs; a Syndrome Characterized by Fat Legs and Orthostatic Edema, Proc. Staff Meet., Mayo Clin. **15**:184 (March 20) 1940.

metric fatty swelling of the legs, frequently including the hips. Women with this syndrome showed a tendency to obesity, and the condition was aggravated during standing, particularly in warm weather, when slight pitting might occur. A family history of large legs was obtained in many instances. The edema was soft and did not involve the feet, and pain could be elicited on pressure. The only complaint other than the appearance of the legs was that of aching distress. In no case was there history of recurrent episodes of acute cellulitis, such as may occur in the course of lymphedema. The basic difficulty in this disorder is chiefly an unusual amount of fat beneath the skin, offering abnormally poor resistance to the passage of fluid into the tissues from the blood. Therapy was usually unsatisfactory, reduction in weight and reassurance being helpful.

TREATMENT

This year the trend in the literature on therapy for peripheral vascular diseases is mainly toward the use of drugs. Little mention is made of the mechanical devices previously so popular. Vitamins and estrogenic substances have finally made their appearance, to be included in the vast therapeutic armamentarium for vascular disturbances.

The dangers associated with the use of many ordinary therapeutic procedures for peripheral vascular diseases have been frequently stressed. Oard, Campbell and Dealy,[91] in a study of 40 patients hospitalized because of peripheral vascular diseases, noted that more than half of them sustained one or more types of injury sufficient to produce an open lesion. There were only 13 instances of trauma resulting from self treatment or accident. The remaining 24 instances of trauma occurred through the advice or at the hands of a professional attendant. Usually injury resulted from some form of ill advised therapy in cases in which circulatory failure was not recognized. The authors warned against the use of overheating, excessive pressure, application of strong chemicals and surgical procedures about corns or ingrown toe nails in patients with vascular disturbances, as open lesions develop easily. These lesions were shown to entail great economic loss to the patient, as well as prolonged morbidity and a high death rate.

Pilcher [92] found that atropine and ephedrine were of little prophylactic value against postoperative thrombosis and pulmonary embolism. He used injections of these drugs routinely in treatment of 406 patients admitted to the hospital because of accident or for operation. Injections were given on the fifth, seventh and ninth days after operation. The

91. Oard, H. C.; Campbell, C. R., and Dealy, F. N.: Traumatic Complications in Peripheral Vascular Disease, Am. J. M. Sc. **199**:194 (Feb.) 1940.

92. Pilcher, R.: Postoperative Thrombosis and Embolism: Report of Trial of Ephedrine and Atropine as Prophylactic, Lancet **1**:752 (April 1) 1939.

incidence of thrombosis and embolism was found to be approximately the same as in a control series of 1,265 cases.

Perlow [93] reported his results in 31 cases of peripheral circulatory disturbances in which he used prostigmine subcutaneously and orally. As this drug has been shown to produce vasodilatation, it was found most valuable as an adjunct in treating circulatory disturbances in which vasospasm existed. The drug was used clinically in 11 cases of thromboangiitis obliterans, 4 of arteriosclerosis, 9 of Raynaud's syndrome, 5 of acrocyanosis and 2 of acute vascular occlusion. Improvement was noted in half the cases, the best results being obtained with thromboangiitis obliterans and Raynaud's syndrome. In the cases of thromboangiitis claudication improved, and in those of Raynaud's disease the number of daily vasospastic attacks diminished. In 4 of 5 cases of acrocyanosis the drug was found to produce warmth in the hands, but little change in color. An initial subcutaneous injection of 0.5 mg. of prostigmine methyl sulfate was given and the degree of vasodilatation noted. During the subsequent week the drug was given by mouth in doses of 7.5 mg. of prostigmine bromide three times a day. If no improvement occurred the dose was doubled. In 1 case, 30 mg. four times a day was given without success. Amounts up to 60 mg. daily were usually tolerated without abdominal cramps. Cessation of action occurred promptly with administration of atropine.

The mechanism of action has been shown by other investigators to be the neutralization of choline esterase, thus permitting the cholinergic substance, normally present, to act at the parasympathetic nerve endings. In the cases of mild primary vasomotor disturbances in the extremities, relief continued as long as prostigmine was administered, with recurrence of symptoms when the drug was stopped.

Weichsel [94] reported excellent results in patients suffering from intermittent claudication with the intravenous administration of calcium salts. All his 25 patients improved subjectively. Evidence of vasodilatation was noted with the plethysmograph. Calcium gluconate, in doses of 10 to 20 cc. of a 10 per cent solution, was originally used, but because of the tediousness of technic, the relative expense and the instability of gluconate, calcium chloride was substituted, with equally good results. The latter drug was administered intravenously by the infusion method in a concentration of 1 or 2 per cent in physiologic solution of sodium chloride. All the patients received 2 Gm. of calcium chloride once a week for twelve weeks. Claudication distance (the distance a patient

93. Perlow, S.: Prostigmine in the Treatment of Peripheral Circulatory Disturbances, J. A. M. A. **114**:1991 (May 18) 1940.

94. Weichsel, H. S.: Studies in Peripheral Vascular Disease: I. Intravenous Calcium in Occlusive Vascular Disease, Ann. Int. Med. **13**:1150 (Jan.) 1940.

could walk before claudication develops) was materially and consistently increased, rest pain and night cramps were reduced and ulcers healed by this form of therapy.

Mulinos, Shulman and Mufson [95] studied the effect of papaverine hydrochloride and histamine iontophoresis in 5 cases of Raynaud's disease. The papaverine was given intravenously in large doses, from 10 to 120 mg., three times a week. The histamine was administered by iontophoresis either before or after the papaverine. Treatment was continuous for from eight to twelve weeks and was terminated by the advent of warm weather. After prolonged treatment the blood flow to the hand increased 33 per cent, and the average hand capacity increased 47 per cent over the preinjection levels. After injection of papaverine, histamine usually decreased the rate of inflow but increased further the capacity of the hand. With the simple plethysmographic method, papaverine was shown to increase the volume of the hand from 5 to an average of 13.8 cc. A further increase was noted when papaverine was given after histamine iontophoresis. The cutaneous temperature increased after the injection of papaverine. No changes in oscillometric readings were noted during a period of forty-five minutes after injection. Cutaneous temperature was decreased after histamine iontophoresis, but this was always elevated after the administration of papaverine. Capillary microscopy revealed an increase in speed of blood flow after injection of papaverine, but histamine not uncommonly lessened the flow.

Clinically, the patients improved under this regimen. Exposure to cold no longer produced syncope, cyanosis and pain in the extremities. Despite the long-continued treatment, little cerebral depression occurred, and no one became addicted to the drug.

Fisher, Duryee and Wright [96] studied the effect of a deproteinated tissue extract on patients suffering from intermittent claudication due to arteriosclerosis obliterans. In so doing, a new apparatus to measure claudication time was described. This consisted of a vertical stand fitted with a foot pedal which, when depressed, raised a weight of 13.6 pounds (6.2 Kg.). The claudication time thus depended on the length of time a given subject was able to use this apparatus at a constant rate of speed. Improvement of claudication time was noted in 23 of a series of 27 patients after the injection of deproteinated tissue extract. This response was as a rule temporary, as after ten or more injections only 19 patients showed improvement; however, the claudication time

95. Mulinos, M. G.; Shulman, I., and Mufson, I.: On the Treatment of Raynaud's Disease with Papaverine Intravenously, Am. J. M. Sc. **197**:793 (June) 1939.

96. Fisher, M. M.; Duryee, A. W., and Wright, I. S.: Deproteinated Pancreatic Extract (Depropanex): I. Effect in the Treatment of Intermittent Claudication Due to Arteriosclerosis Obliterans, Am. Heart J. **18**:425 (Oct.) 1939.

in this series was prolonged to an average of more than three times that of the control subject. Physiologic solution of sodium chloride substituted for the extract failed to produce an increase in claudication time under identical conditions.

Meleney [97] stressed the importance of bacteriologic studies of the involved areas in cases of diabetic gangrene. Although the infected areas usually contain a mixture of organisms, aerobic and anaerobic cultures should be taken as an aid to surgical judgment, as well as a guide to specific therapy against the predominant organism. Meleney stated that zinc peroxide markedly inhibits the growth of the hemolytic streptococci and all anaerobic bacteria, including the organisms causing gas gangrene and anaerobic streptococci. It neutralizes or inactivates the toxins formed by these organisms and at the same time encourages the reparative process by the stimulation of granulation tissue. Zinc peroxide, which is a white powder, should be suspended in sterile distilled water and applied to every part of the surface of the wound. The author found this drug an effective antiseptic to minimize the possibility of the establishment of infection at the time of the primary injury and a means of continuing surface protection. If hemolytic streptococci and anaerobic organisms are present at the site of amputation, zinc peroxide is advised as a prophylactic to prevent the development of infection in the stump, or if infection has developed the drug should be used as early as possible to control it.

Herrmann and McGrath,[98] in the treatment of 16 patients with arterial insufficiency due to secondary vasomotor instability, associated with active arteritis or phlebitis, used moderate quantities of estrogen parenterally (estrone, or theelin) at regular intervals for at least sixteen weeks. The final evaluation of the patient's condition was based on objective studies of the efficiency of the peripheral vascular system and on an analysis of the patient's account of the effects on the signs and symptoms of the disease of a variety of environmental conditions. Twelve patients who had pronounced pain were given moderately large amounts (50 mg. intravenously each day for five days) of thiamine chloride, in addition to the estrogenic substances. Eleven of the 16 patients were so much improved that they were able to return to their work. Either the vasomotor instability completely disappeared or the disease process remained so quiescent that it caused no great disability or concern. Pain in the digits showed equal improvement. Vascular studies on these patients showed a more nearly normal response of the blood vessels

97. Meleney, F. L.: The Use of Zinc Peroxide in the Treatment of Diabetic Gangrene of the Lower Extremities, Surgery **6**:845 (Dec.) 1939.

98. Herrmann, L. G., and McGrath, E. J.: Effect of Estrogens on Vascular Spasm Due to Active Angiitis in the Extremities, Arch. Surg. **40**:334 (Feb.) 1940.

under natural environmental conditions and in a room at constant temperature. Three patients had a recurrence of the signs and symptoms after two years of relief, but the activity of the process again subsided, though less completely, after another course of treatment with estrogen. The symptoms of 4 of the remaining patients have remained unchanged after many months of observation, and those of the last patient have continued to grow worse, in spite of all therapeutic effort.

Edwards, Hamilton and Duntley [99] made a preliminary report on the effect of crystalline testosterone propionate in the treatment of 7 male patients suffering from organic vascular disease. Three of the men presented typical signs of thromboangiitis obliterans, and the other 4 were arteriosclerotic. In all 7 patients the involvement was major, with loss of the popliteal, the femoral and, in 1 case, the iliac pulsations. The signs and symptoms were marked, including small ulcerations in 2 of the patients with thromboangiitis obliterans. The testosterone propionate, dissolved in peanut oil, was given intramuscularly two or three times a week. Adjunctive treatment consisted only of general hygiene, except in the case of the ulcer-free patient with thromboangiitis obliterans, who received eight hours of suction pressure treatment. None of the patients was followed for more than several months. In each of the patients spectrophotometric examination showed lack of arterialization of the skin, which involved not only the diseased limbs but also the entire body. Administration of testosterone propionate produced an early and decided arterialization of the cutaneous blood. Moreover, the after-treatment curves likewise showed an inconstant diminution in the volume of blood in the more venous areas of the body. Other objective evidence of favorable change was an increase in the systolic pressure of from 6 to 26 mm. of mercury in the hypotensive members of this group and lowering of the pressure in 2 patients with hypertension. The ulceration in 1 patient with thromboangiitis obliterans was healed; in the second it was greatly improved. There was marked improvement in the walking ability of all the patients, with delay or abolition of intermittent claudication. Two patients were no longer subject to night pain. Subjectively, the patients reported increased activity and a feeling of optimism, results similar to those reported previously with this treatment.

Ochsner and Smith [100] were able to control the pain of varicose ulcers with rather large doses of vitamin B_1, thus confirming the recent work

99. Edwards, E. A.; Hamilton, J. B., and Duntley, S. Q.: Testosterone Propionate as Therapeutic Agent in Patients with Organic Disease of Peripheral Vessels: Preliminary Report, New England J. Med. **220**:865 (May 25) 1939.

100. Ochsner, A., and Smith, M. C.: The Use of Vitamin B_1 for the Relief of Pain in Varicose Ulcers, J. A. M. A. **114**:947 (March 16) 1940.

of European investigators. The dose suggested was 5 mg. three times a day, to be doubled within three or four days if relief from symptoms did not occur. Ten patients received this vitamin, in the form of thiamine chloride, orally. Within an average of five days complete relief was obtained. In 5 of the 10 patients there was, in addition to the relief of symptoms, definite improvement in the healing of the ulcer, even though the condition had been resistant to therapy prior to vitamin administration. No explanation for the rationale of this therapy was given, except that the patients possibly were deficient in vitamin B_1.

The value of synthetic vitamin B_1 in treatment of painful amputated stumps was reported by Sliosberg.[101] It is discussed in the surgical review.

The value of heparin in vascular diseases is also considered in the surgical section of this review. Mention, however, will be made at this time of its value in thrombophlebitis, as described by Murray.[102] He found it of value in the treatment of this disease as it prevented further extension of thrombosis and allowed healing to take place.

Articles favorable to the revival of Buerger's exercises are worthy of mention. These exercises consist either of activity performed by the patient, as originally described, or of passive movement with the oscillating bed.

Kaiser[103] was able to improve the circulation in the distal portion of the extremities in 19 cases of peripheral vascular disease associated with diabetes with Buerger's exercises as the sole form of treatment. The exercises described vary but little from the original save in time limits, those of each, particularly the rest period, being slightly extended. As an example, the dependent portion was maintained for one minute longer than was necessary for complete rubor to occur, usually from two to five minutes. The rest periods in the horizontal position lasted five minutes. Each cycle lasted about ten minutes, and the patient started with three cycles three times a day, increasing one cycle per day until every other waking hour was devoted to exercises. With this regimen alone 4 of 5 patients with ulcers only were improved, and 11 of 14 without ulcers but with vascular symptoms had relief. Most of the failures were found among uncooperative patients or those with complications. No mention was made of whether the patient was ambulatory or confined to bed.

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101. Sliosberg, R.: Le traitement des algies des amputés par la vitamine B_1 synthétique, Presse méd. **47**:1585 (Dec. 6-9) 1939.

102. Murray, G.: (*a*) Heparin in Surgical Treatment of Blood Vessels, Arch. Surg. **40**:307 (Feb.) 1940; (*b*) Heparin in Thrombosis and Embolism, Brit. J. Surg. **27**:567 (Jan.) 1940.

103. Kaiser, H. L.: Buerger's Exercises for Diabetic Patients with Peripheral Vascular Diseases, Physiotherapy Rev. **20**:18 (Jan.-Feb.) 1940.

Barker [104] found the oscillating bed to be a valuble adjunct to therapy in 85 cases of peripheral occlusive disease. The physiologic effects noted were (1) definite rhythmic changes in color of the feet and toes, namely, pallor when elevated and rubor when dependent, indicating alternate emptying and filling of the capillary bed; (2) rather striking and rapid relief of pain of vascular origin in a large number of cases during the time that the patient was in the bed; (3) induction of sleep in a large number of cases, even when the patient had had great difficulty in sleeping for some time, and (4) definite but complete vasodilatation, as evidenced by a rise in the cutaneous temperature of the digits. Patients with intermittent claudication received little or no benefit. Of 13 patients with so-called rest, or pretrophic, pain, without ulceration or gangrene, 12 obtained relief during treatment, but it was maintained only in 11 of these patients after treatments were discontinued. Complete and sustained relief of pain was obtained in 9 of 15 patients with ischemic neuritis.

Of the 44 patients with ulceration, gangrene and severe pain, 32 received relief of pain while in the bed, but only 22 maintained this improvement after treatment was discontinued. In these 22 cases the gangrene and ulcerative lesions healed. Specific treatment, with the oscillating bed, was used in some of these cases. Barker expressed the opinion that the oscillating bed is a valuable addition to the armamentarium in the treatment of peripheral vascular disease but should not supplant the other methods now used, as it can be readily used in conjunction with them.

Kramer [105] treated a series of 103 patients with intermittent venous occlusion. In all, about 1,500 treatments were given. The results in the group with Buerger's disease and arteriosclerosis with diabetes were average, 66.6 per cent of patients being benefited. The results in the group with arteriosclerosis without diabetes were disappointing, being favorable in 60 per cent. The largest series consisted of 33 patients with phlebitis. In these patients symptoms were due mainly to reflex vasospasm and were favorably influenced in 72.8 per cent. The results of this type of therapy were evaluated through improvement in symptoms. Eighty-five per cent of the patients obtained relief from fatigue, 77 per cent from cramps and 71 per cent from pain. In the entire series, 70 patients were thought to be benefited.

104. Barker, N. W.: The Use of Oscillating Beds in the Treatment of Peripheral Occlusive Arterial Disease, Proc. Staff Meet., Mayo Clin. **14**:618 (Sept. 27) 1939.

105. Kramer, D. W.: Intermittent Venous Compression in the Treatment of Peripheral Vascular Disorders, Am. J. M. Sc. **197**:808 (June) 1939.

ARTERIAL HYPERTENSION

The committees [106] for the standardization of blood pressure readings of the American Heart Association and the Cardiac Society of Great Britain and Ireland have recommended a standard procedure for the measurement of arterial blood pressure. The need for a definite procedure is obvious, as wide variations in technic and interpretation have been noted among different groups of physicians, teachers and life insurance examiners and students.

Especially to be noted are the preparation and position of the patient and the method of application of the cuff. Lack of care in these fundamentals often results in conspicuous errors. Likewise, the proper care and inspection of the apparatus for sources of error are of utmost importance. The possibilities of error due to faulty equipment are great.

The patient should be lying or sitting comfortably and relaxed. The cuff, completely deflated, should be applied to the inner side of the arm, snugly and evenly, with the lower edge about 1 inch (2.5 cm.) above the antecubital space. The cuff should be applied smoothly and in such a way that neither bulging nor displacement occurs. It is recommended that palpation be used as a check on the auscultatory readings. The pressure should be raised in steps of 10 mm. of mercury until the radial pulse ceases and then be allowed to fall rapidly. The higher of the two readings, palpatory or auscultatory, should be accepted as the systolic pressure. The bell of the stethoscope should be applied over the previously palpated brachial artery in the antecubital space with a minimum of pressure to secure complete apposition to the skin. The pressure in the cuff should be raised about 30 mm. of mercury above the level at which the radial artery can be felt and then deflated at the rate of 2 to 3 mm. per second. The level at which the first sound appears is to be considered the systolic pressure unless the palpatory level is higher. As the cuff is still further deflated, the point at which the sounds suddenly become muffled should be considered the diastolic pressure. If this point and that at which the sounds entirely disappear are not the same, the American committee recommends that the latter also be considered as the diastolic pressure and that both readings be recorded. This may be expressed as 140/80-70 or 140/70-0. The cuff should be completely deflated before any other readings are made.

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106. Standard Method for Taking and Recording Blood Pressure Readings, by Committee for the Standardization of Blood Pressure Readings of the American Heart Association and the Committee for the Standardization of Blood Pressure Readings of the Cardiac Society of Great Britain and Ireland, J. A. M. A. **113**: 294 (July 22) 1939.

Physical and psychologic factors are to be considered. The relation to blood pressure readings of exercise, intake of food, emotional state of the patient and time of day is important. The possibility of variations in the two arms should be remembered. In the presence of cardiac arrhythmias blood pressure readings are inaccurate at best. Extrasystoles in which the systolic pressure is higher than average should not be considered as the systolic pressure. With auricular fibrillation, it is suggested that an average of several readings is necessary even to approximate a blood pressure reading.

Further suggestions are made in the report of the committees. This report should be read in its original form by all students.

Robinson and Brucer [107] made a statistical study of a very large group of persons in an attempt to establish a more accurate notion of what constitutes normal blood pressure. They are somewhat caustic in their comment on the opinions of other observers, and in some respects are probably on the right path. At any rate, the study is an extensive one, and well done, and deserves consideration and thought. The authors concluded that the normal range of the systolic blood pressure is from 90 to 120 mm. of mercury and that of the diastolic from 60 to 80 mm. Almost two thirds of all blood pressure readings for the total group were below 125 systolic and 80 diastolic.

They pointed out that there is no such disease entity as hypertension and that in the absence of other findings, which should be carefully ruled out, a low pressure is an ideal blood pressure. With this view there can be but little disagreement. The fallacy concerning the rise in blood pressure with age was also emphasized. Prehypertensive blood pressures, as well as definite hypertensive pressures, do increase with age. The blood pressure of the normal person becomes more or less stabilized at adolescence and remains fairly constant throughout life. The lower the average blood pressure level, the less variation in pressure is noted. Pressures below 120 mm. of mercury systolic are less variable and erratic than pressures above 120 mm. Pressures below this level are more likely to retain a constant level, while those above tend to increase with age. The authors stated that the upper limit of normal for systolic pressure is 120 mm. of mercury.

This raises the question of what significance is to be attached to pressures slightly higher than normal. Certainly they should not be considered as indicative of hypertension. There are many conditions in which a slight rise of blood pressure is symptomatic. It should also be remembered that such figures as have been arrived at by the authors

107. Robinson, S. C., and Brucer, M.: Range of Normal Blood Pressure: A Statistical and Clinical Study of 11,383 Persons, Arch. Int. Med. **64**:409 (Sept.) 1939.

indicate a general trend and cannot be applied directly to each person as an inflexible rule. There are no doubt many exceptions, although the statement is made that the history of a blood pressure of over 120 systolic and 80 diastolic for a ten year span "is almost an infallible sign of incipient hypertension."

The authors stated: "Slightly more than 40 per cent of the adult population is either actually or incipiently hypertensive." If the author's conclusions in this respect are to be accepted, the number of persons who must be regarded as hypertensive will be tremendously increased, and 40 per cent seems a conservative figure. A second question arises: What is meant by the authors' term "incipient hypertension"? In the conclusions no mention is made of the etiologic factors involved in increased blood pressure or of the various patterns.

It is true that this work is provocative; from its nature, it is important that further similar studies be made. A defect in this paper is the consideration of blood pressure readings without regard to the cause of increased pressure. It is the analysis of a single symptom treated as an entity.

Schroeder and Steele [108] have attempted to classify a group of cases of essential hypertension according to the significant phenomena presented in each case. The purpose is apparently to suggest an etiologic relationship. They grouped these cases on the basis of disturbances in the renal, nervous, endocrine and vascular symptoms. There was a fifth group which could not be classified. They regarded as suggestive the fact that hypertension can be produced experimentally in animals by disturbing one or the other of at least three of the four systems.

The first group included cases of glomerulonephritis, pyelonephritis, bilateral hydronephrosis, persistent polyuria and other renal abnormalities. In the second group, of the symptoms related to the central nervous system which were encountered, the diencephalic syndrome accounted for a fair portion of the cases. Vasomotor instability, autonomic instability and endocrine factors were present in several of the other cases. Symptoms of this type were usually found in young women, in a few instances in older women and only occasionally in men. Significant changes in the eyegrounds were rare in this group. Evidence of some endocrine disturbance was present in 41 women and 2 men of the third group. Basal metabolic rates were elevated in the absence of obvious goiter in some patients, while others were definitely thyrotoxic at the onset of the hypertension. In 9 of this group, the onset of the increase in blood pressure occurred at the menopause. Obesity and hypertrichosis were also manifestations. Cushing's syndrome was present in 3 of the endocrine group.

108. Schroeder, H. A., and Steele, J. M.: Studies on "Essential" Hypertension: I. Classification, Arch. Int. Med. **64**:927 (Nov.) 1939.

Arteriosclerosis was the most common factor, other than hypertension. In the unclassified group were those cases in which hypertension began during pregnancy and the cases of malignant hypertension. The significance of this grouping is uncertain.

Williams and Harrison [109] also attempted to classify hypertension under various syndromes according to the probable underlying and aggravating causes. This could not be done with certainty, but in most cases they found one or more factors which seemed to offer opportunity for the alleviation of symptoms at least. Group 1 represented cases of neurogenic origin; group 2, cases of endocrine disturbance; group 3, cases of renal hypertension, including acute and chronic nephritis, urinary obstruction, disease of the renal arteries and tumors; group 4, cases of metabolic hypertension and hypercholesteremia with renal atheroma and gout; group 5, cases of hypertension caused by congestive heart failure (which is open to question), and group 6, unclassified cases.

Many of the conditions which have been listed seem to produce hypertension only when they occur in predisposed subjects.

Ivy and McEwen [110] discussed in outline form some of the physiologic aspects of hypertension. Both increased peripheral resistance in the arteriolar bed and loss of elasticity in the larger arteries are probably essential factors in clinical hypertension. These factors in an artificial circulation experiment resulted in variations in pressure similar to those found in clinical hypertension. The authors asserted that the essential factors in experimental hypertension were produced by renal ischemia. They expressed the belief that ischemia of other abdominal viscera is not a factor and that the nervous system is not involved in the Goldblatt type of hypertension. Of the endocrine glands, only the adrenal cortex is necessary for the manifestation of increased blood pressure. There is at least presumptive evidence that the hypertension is due to a humoral agent of renal origin and that hypertension of both the so-called benign and the malignant type can be produced in Goldblatt animals. The question of the nature of the probable pressor substance was considered. That it is an intermediate product of an enzyme acting on a substrate present in the blood seems possible. Another alternative is that the renal hypertensive substance is not a vasoconstrictor per se but acts in conjunction with other hormones or substances. It is also possible that the renal substance may neutralize some

109. Williams, J. R., Jr., and Harrison, T. R.: Clinical Pictures Associated with Increased Blood Pressure: A Study of One Hundred Patients, Ann. Int. Med. **13**:650 (Oct.) 1939.

110. Ivy, A. C., and McEwen, E. G.: A Physiological Consideration of Certain Aspects of Hypertension, Quart. Bull. Northwestern Univ. M. School **14**:72, 1940.

depressor substance normally present in the blood, or that it may be an arteriolar toxin which gradually causes degenerative changes in the arteriolar wall.

That renin is inactive as a vasoconstrictor substance except in the presence of whole blood, plasma or erythrocyte protein was shown by the continued experiments of Page and his associates.[111] This activating substance is thermolabile. It is also present in increased amounts in the plasma of dogs with experimental hypertension.

Rodbard and Katz [112] conducted experiments on dogs which indicated that the renal pressor substance was rapidly excreted, lost or destroyed when the ischemic kidney was removed and a normal kidney remained, but if the normal kidney had been previously removed the increased blood pressure was found to endure about five times as long. Normal blood pressure has no relation to the kidney, but "renal hypertension depends upon the kidney for its genesis, continuation and elimination."

With this view Williams, Diaz, Burch and Harrison [113] expressed essential agreement—that is, that renin plays no role in regulating normal blood pressure. They also found in their experiments on rats that the hypertension in hypophysectomized animals is not related to the renal pressor substance, or that if such a relationship exists it must be mediated through some unknown mechanism. They found no relation between the gonads and blood pressure.

The animals which were adrenalectomized showed a fall in blood pressure, although they were kept alive by means of the administration of a solution of sodium chloride. They were markedly less sensitive to renin than were normal animals. The kidneys of these animals contained as much renin as did those of normal animals by the methods of assay used by the authors. The same was found to be true in the hypophysectomized animals.

Stead and Kunkel [114] noted that in normal human subjects paredrinol produces a type of hypertension resembling closely that observed in disease. The average duration after intramuscular injection of 25 mg. of the drug is one hour. In addition to hypertension, there are slowing of the heart rate, increased vigor of the apex impulse and appearance of

111. Kohlstaedt, K. G.; Page, I. H., and Helmar, O. M.: The Activation of Renin by Blood, Am. Heart J. **19**:92 (Jan.) 1940.

112. Rodbard, S., and Katz, L. N.: Elimination of the Effect of the Chemical Mediator of Renal Hypertension, Ann. J. M. Sc. **198**:602 (Nov.) 1939.

113. Williams, J. R., Jr.; Diaz, J. T.; Burch, J. C., and Harrison, T. R.: The Relation of the Adrenal Glands to the Action of the Renal Pressor Substance, Am. J. M. Sc. **198**:212 (Aug.) 1939.

114. Stead, E. A., Jr., and Kunkel, P.: Mechanism of the Arterial Hypertension Produced by Paredrinol, J. Clin. Investigation **18**:439 (July) 1939.

loud heart tones. The effect is not always constant. The rate of blood flow in the dilated hand is moderately decreased, as are the fluctuations in vasomotor tone in the hand and foot. A rise in venous pressure occurs, and the T waves of the electrocardiogram are increased. The cardiac output, circulation time and basal metabolism are not significantly altered.

The decrease in heart rate is an effect of the vagus nerve resulting from stimulation of the carotid sinus and aortic nerves. This can be removed by the administration of atropine. When atropine is given, the heart rate is increased and the blood pressure, particularly the diastolic, rises to higher levels. The rise in pressure can be controlled by the use of nitrites and by placing the patient in the upright position. The authors expressed the opinion that both a direct vasoconstrictor effect on the peripheral vascular bed and an increase in venous tone are factors.

Iglauer and Altschule [115] concluded that both benzedrine and paredrine cause a rise in blood pressure by increased arteriolar vasoconstriction. They found that the pressor effects persist after the paralysis of the vasomotor nerves which occurs with spinal anesthesia. In their opinion, the evidence indicates that the smooth muscle of the arterioles is the site of action of these drugs.

Taquini [116] demonstrated the presence of a pressor substance produced by the totally ischemic kidney if the occlusion of the renal pedicle is temporary. This work was done on dogs, and the results were fairly uniform. After establishment of the circulation, a rise in blood pressure took place. Taquini concluded that the rise in pressure which occurs under these conditions is the result of the elaboration of a substance found during the period of total ischemia. This substance acts directly on the peripheral vessels, and hypertension is produced by the peripheral vasoconstriction which is induced by this direct action of this substance on the walls of the blood vessels.

Major and his associates [117] reported on continuation of their work on "blood guanidine." They found an increase of this substance in the blood of animals in which arteriovenous fistula of the renal arteries and veins was created. This increase in "guanidine" was found in animals with experimental renal insufficiency both with and without accompanying hypertension. The exact chemical nature of this "guanidine-like substance" is still not definitely determined.

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115. Iglauer, A., and Altschule, M. D.: The Pressor Action of Benzedrine and Paredrine, Am. J. M. Sc. **199**:359 (March) 1940.

116. Taquini, A. C.: The Production of Pressor Substance by the Totally Ischemic Kidney, Am. Heart J. **19**:513 (May) 1940.

117. Major, R. H.; Weber, C. J., and Rumold, J. J.: Blood "Guanidine:" Further Observations, Arch. Int. Med. **64**:988 (Nov.) 1939.

In an attempt to evaluate the cold pressor test, Thomas and Warthin [118] subjected dogs, both those with normal pressures and those in which hypertension had been induced, to a standard cold stimulus. In the normal dogs there was no response which could be interpreted as a pressor reaction, although some showed a rise in blood pressure, which tended to diminish as the animals became trained to the procedure. In 87 per cent of the group with renal hypertension the results of the tests were reported as negative. In the animals in which hypertension was induced by buffer nerve section the reaction to the cold test was variable, more often negative than positive. In none of the animals was there a reaction analogous to that in man. The authors concluded that experimental hypertension in dogs produced by renal ischemia is more nearly analogous to the hypertension of renal disease in man than to essential hypertension. Physiologically this seems probable and is in agreement with the results of Miller and Bruger,[119] who made cold pressor observations on normal persons and on those with renal hypertension, as well as on patients with essential hypertension. They found that the patients with chronic nephritis gave a response similar to that of normal subjects who did not show hyperreactions. There was a slight rise in blood pressure above that of normal persons in this group. Thirty-nine per cent of the normal group gave hyperreactions, and 76 per cent of the group with essential hypertension had a significant rise in pressure in response to the test. Among the older patients with essential hypertension, in whom arteriosclerosis, albuminuria and other evidences of renal disease were present, the pressor response was not as marked as in the younger members of this group.

Hines,[120] in a discussion of the significance of vascular hyperreaction as measured by the cold pressor test, stressed again the technic of the procedure. It is generally conceded that quick rises in blood pressure unassociated with increase in heart rate or cardiac output are the result of increased peripheral resistance, which in turn is the result of vasoconstriction in the arteriolar bed. The rise in blood pressure following the cold pressor test may be regarded as an index of vascular reactivity. It is pointed out that, as in all clinical tests, there is a certain amount of normal individual variation, but that if care is taken to secure the same basal conditions and to follow the same technic, essentially the same response is elicited in the same subject in repeated tests. Varia-

118. Thomas, C. B., and Warthin, T. A.: The Response of Normal Dogs and Dogs with Experimental Hypertension to a Standard Cold Stimulus, Am. Heart J. **19**:316 (March) 1940.

119. Miller, J. H., and Bruger, M.: The Cold Pressor Test in Normal Subjects and Patients with Primary (Essential) and Secondary (Renal) Hypertension, Am. Heart J. **18**:329 (Sept.) 1939.

120. Hines, E. A., Jr.: The Significance of the Vascular Hyperreaction as Measured by the Cold Pressor Test, Am. Heart J. **19**:408 (April) 1940.

tions in the response to the test resulting in discrepancies of interpretation can be explained, according to Hines, by variations in the technic of the test. The diastolic response to the stimulus is regarded as a more reliable index of vasoconstriction than the systolic. Both systolic and diastolic rises should be considered in evaluating the result. A significant response was regarded by Hines to be a rise of more than 20 mg. of mercury systolic and of more than 15 mm. diastolic. Such an increase above the basal level would indicate a hyperreactive vasoconstrictor mechanism.

Of persons whose blood pressure was usually normal, Hines found a mean systolic rise in the older age group. The mean diastolic response of children with normal blood pressure was increased, but that of persons more than 50 years of age was decreased. Persons with essential hypertension showed a mean diastolic response which was about the same at all ages.

The response of persons with hypertension was from two to six times as great as that of persons whose blood pressure was usually normal, and in some subjects it was extreme. It has been found that in patients in whom hypertension is developing the response is unusually marked. Hines expressed the belief that this hyperactivity is an important etiologic factor in essential hypertension.

A significant increase in the response was found in a group of persons who were known to have had hypertension in the past but whose blood pressure was normal at the time of the test. The same was true of persons who showed signs of hypertension in the fundi but whose blood pressure was usually normal. These persons were regarded as having latent hypertension. It appears from the work of Hines and others that vasoconstrictor hyperreaction may be regarded as an inherited characteristic. There appears to be a correlation between a hyperreactor response to the cold pressor test and the increased response to nervous or psychic stress, such as is sometimes noted in an initial blood pressure reading, which is commonly found to be higher than the average recorded subsequently.

Stead and Kunkel [121] found a uniform increase in peripheral resistance in all parts of the body. It could not be reduced to normal in the skin of the extremities, in the muscles of the forearm or in the brain by vasodilating stimuli. Measurement of the blood flow in the foot of a person with essential hypertension showed no change after malaria, although a marked fall in arterial pressure occurred. This was interpreted to mean that there had been no structural change in the vessels. Another patient observed under similar conditions showed a decrease in blood flow with the fall in arterial blood pressure. This

121. Stead, E. J., Jr., and Kunkel, P.: The Nature of Peripheral Resistance in Arterial Hypertension, J. Clin. Investigation **19**:25 (Jan.) 1940.

was interpreted as indicating extensive structural alteration in the vessel wall, although vasoconstriction was probably the initial factor responsible for hypertension.

Vasoconstrictor responses to sensory stimuli remained the same in spite of the fall in blood pressure with malaria. This identical response was found also in some normal subjects, as well as in persons with essential hypertension.

Engle and Binger [122] made observations on the effect on blood pressure of acetylbetamethylcholine in persons with hypertension and in normal persons. Their findings support the hypothesis that a deficient acetylcholine vasodilator mechanism may be a factor at least in some types of arterial hypertension. In support of this view, a definitely greater percentage decrease in blood pressure was found in persons with essential hypertension than in normal persons. The dose of the drug, injected subcutaneously, was 2.5 mg. Little or no change was noted in normal persons, while in patients with hypertension a well marked fall occurred, amounting to three or four times that of normal subjects. A rise in heart rate corresponding to the fall in blood pressure was noted. This occurred in all types of hypertension.

When the cold pressor test was applied after administration of the drug it was found that the vasoconstrictor response was markedly decreased. Conversely, there was a more marked fall in blood pressure with this drug than was observed during anesthesia induced by the intravenous injection of pentothal sodium (sodium ethyl 1-methylbutylthiobarbiturate).

It is interesting to note that dogs in which hypertension had been induced by renal ischemia showed no greater fall in blood pressure after the drug was administered than did normal dogs. This illustrates another point in which experimental renal hypertension differs from essential hypertension in man.

It is curious that persons with the hypertension of chronic glomerulonephritis should show nearly as marked a fall in pressure in response to the injection of acetylbetamethylcholine as do persons with essential hypertension.

The reaction seems to be peculiar to hypertension. A small group of subjects were tested in whom there had previously been a fall in blood pressure from a hypertensive to a normal level. These subjects showed a much greater response to the drug than did normal persons.

It would seem that this approach to the problem of hypertension is important and that it deserves much more consideration, as the authors have stated in conclusion.

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122. Engle, D. E., and Binger, M. W.: The Response in Blood Pressure of Hypertensive Patients to Acetyl-Beta-Methylcholine, Am. J. M. Sc. **198**:609 (Nov.) 1939.

Wagener and Keith,[123] in an excellent discussion of the problem of hypertension, arteriolar disease and the associated retinal lesions, have led one to believe that regardless of the original initiating factor, whether inflammatory renal disease or functional arteriolar spasm, persistent hypertension is probably of renal origin. Anatomic lesions in the arterioles of the kidneys seem to be the primary site of origin of the hypertension syndrome. In the more rapidly progressive form lesions are present in the endothelium. The authors suggested that such changes may be the result of spasm, persistent and severe, in these vessels. When this occurs the picture which they have termed malignant hypertension is present. They repeated their classification of the hypertension syndrome under four types, using the same basis as they had previously employed. The differentiation seems somewhat clearer and better defined in the light of more recent knowledge.

However, the underlying, and perhaps the most important, idea advanced is that hypertension may result from primary renal disease, as well as when no primary or secondary lesion of the kidneys is present. The rise in blood pressure may be acute and of short duration in both types. When this is true the tendency is for the blood pressure to return to normal. When the blood pressure remains elevated in cases of chronic glomerulonephritis, diffuse lesions of the arterioles can be shown both in the retina and in other structures. In all cases included in the study diffuse vascular lesions of these types were present. There was no relation to the size or the functional capacity of the kidneys.

Unilateral pyelonephritis with advanced vascular lesions may or may not be associated with hypertension. The authors stated that because the vascular lesions in pyelonephritis are similar to those in malignant nephrosclerosis there is a tendency for the hypertension in pyelonephritis, when it does occur, to be severe. In fact, they stated that pyelonephritis is responsible for 15 to 20 per cent of the cases of malignant hypertension. The vascular lesions in this disease are restricted to the kidneys, in contrast to those seen in the vascular type of malignant hypertension, in which the disease process is diffuse.

The importance of diffuse arteriolar disease is again emphasized. It results in hypertension of the Goldblatt type and is often amenable to treatment. It was said by the authors to be more common than chronic glomerulonephritis.

Schroeder and Fish [124] reported on 7 patients with arterial hypertension who had associated unilateral organic disease of the kidneys.

123. Wagener, H. P., and Keith, N. M.: Diffuse Arteriolar Disease with Hypertension and the Associated Retinal Lesions, Medicine **18**:317 (Sept.) 1939.

124. Schroeder, H. A., and Fish, G. W.: Studies on "Essential" Hypertension: III. Effect of Nephrectomy upon Hypertension Associated with Organic Renal Disease, Am. J. M. Sc. **199**:601 (May) 1940.

These patients were subjected to nephrectomy. Two improved remarkably and 2 slightly; the rest did not improve. The authors stated that if nephrectomy is to be of definite benefit in such cases the hypertension must have been of short duration and the arteriolar sclerosis of the other kidney in an early stage. This seems to be an important observation.

Dicker,[125] from the observation and careful study of 2 patients, concluded that for the kidneys to cause hypertension the renal circulation must be constricted. All the other renal and urinary manifestations are secondary and play no part in the hypertension, even though fatal renal insufficiency may exist.

Goldbloom and Lieberson[126] reported 3 cases of malignant nephrosclerosis proved at autopsy in which during life examination of the fundi failed to show any evidence of edema of the optic disk, although the other signs of angiospastic retinopathy were present. Such observations are probably not as uncommon as has been generally thought.

Kvale, Allen and Adson[127] reported studies on the circulation time in persons with hypertension. They found it essentially the same as in normal subjects except that the "arm to foot" time was slightly increased. They suggested that there might be some diminution of blood flow to the feet in essential hypertension.

Rosenberg[128] made a careful study of the brains of 17 persons whose death was caused by the phenomena of malignant hypertension. It is important to note that transient cerebral phenomena have been often designated by such terms as cerebral vascular crises and hypertensive encephalopathy. In this group of cases these symptoms were associated with widespread pathologic lesions within the brain. Such transient phenomena have frequently been considered to be caused by arterial or arteriolar spasm. Rosenberg again called attention to the fact that such phenomena are probably based on organic vascular defects. He found that there were three main types of cerebral symptoms in this group of cases: (1) those of increased intracranial pressure, (2) those resulting from multiple miliary cerebral lesions and (3) those of large vascular accidents. Combinations of these types constitute a fourth group. Increased intracranial pressure usually results

125. Dicker, E.: The Role of the Kidney in the Reduction of Arterial Hypertension, Am. J. M. Sc. **199**:616 (May) 1940.

126. Goldbloom, A. A., and Lieberson, A.: Renal Arteriolonecrosis Without Papilledema, Am. J. M. Sc. **198**:52 (July) 1939.

127. Kvale, W. F.; Allen, E. A., and Adson, A. W.: The Rate of Circulation in the Arteries and Veins of Man: II. Studies of Hypertension and Orthostatic Hypotension and the Effects of Sympathectomy, Am. Heart J. **18**:537 (Nov.) 1939.

128. Rosenberg, E. F.: The Brain in Malignant Hypertension: A Clinicopathologic Study, Arch. Int. Med. **65**:545 (March) 1940

from intracerebral or extracerebral edema. The symptoms noted were severe headaches, nausea and vomiting, mental dulness and drowsiness. The symptoms due to multiple destructive miliary lesions were widespread and of varying nature, depending on the portion of the brain involved. Transient hemiplegia and paraplegia, personality changes, fatigue and olfactory hallucinations were among those noted. In the event of extensive cerebral vascular accidents the expected symptoms were found. In all cases the cerebral arterioles were markedly altered. There were an increase in the thickness of the wall and reduction in the caliber of the lumen.

Master, Dack and Jaffe,[129] in an analysis of 500 cases of myocardial infarction, found that hypertension occurred in more than one half of the men and four fifths of the women. They concluded that hypertension is a definite etiologic factor in coronary occlusion. This incidence was definitely greater in their group of cases than that noted in the general population. It occurred five to eight times as often among men with hypertension as among patients with normal blood pressure. Both ratios increase with age in the same proportion.

Newburger and Peters [130] reported 4 cases of capillary glomerulosclerosis and reviewed the clinical records in previously reported cases. Diabetes, hypertension and albuminuria constitute the features of this syndrome, although edema, heart failure, renal failure and anemia are often present. Hypertension was present for varying periods in all the cases. It usually endured for a considerable period, and in all but 1 case was present as one of the initial findings. It often was of rather severe grade.

Goldblatt, Kahn and Hanzal [131] made observations on the constriction of the abdominal aorta just above the site of origin of both main renal arteries. Little or no immediate effect on blood pressure in the vessels above the site of the clamp was noted, but in about twenty-four hours hypertension developed. Below the site of the clamp a fall in pressure occurred in the femoral arteries. Within twenty-four hours the mean pressure in the femoral artery also began to rise, at the same time that the pressure in the carotid artery increased. In some animals the pressure in the femoral artery rose to a level higher than normal,

129. Master, A. M.; Dack, S., and Jaffe, H. L.: Age, Sex and Hypertension in Myocardial Infarction Due to Coronary Occlusion, Arch. Int. Med. **64**:767 (Oct.) 1939.

130. Newburger, R. A., and Peters, J. P.: Intercapillary Glomerulosclerosis: A Syndrome of Diabetes, Hypertension and Albuminuria, Arch. Int. Med. **64**: 1252 (Dec.) 1939.

131. Goldblatt, H. A.; Kahn, J. R., and Hanzal, R. F.: Studies on Experimental Hypertension: The Effect of Construction of the Abdominal Aorta Above and Below the Site of Origin of Both Main Renal Arteries, J. Exper. Med. **69**:649 (May) 1939.

even though the abdominal aorta was occluded. If the aorta was constricted below the site of origin of the renal artery there was no rise in blood pressure above the level of the clamp. The pressure below usually fell and tended to remain low. The authors concluded that the rise in blood pressure occurring under these conditions is due to renal ischemia, regardless of the presence of renal insufficiency.

The number of clinical reports [132] of cases in which disease of the renal arteries in man is associated with hypertension, as well as with urologic types of hypertension, seems to be increasing as the relationship between such disorders is more widely recognized. It is becoming apparent that in all cases of early hypertension disease of the renal arteries should be considered and excluded.

Weiss and Parker [133] have written an excellent monograph on pyelonephritis and have emphasized the relation of persistent hypertension to the chronic and healed forms of the disease, with which arterial hypertension is frequently associated. It may be associated with adequate or impaired renal function, and it is often of severe grade, with all the characteristic findings and symptoms. It is important to note that hypertension did not occur with renal tuberculosis or hydronephrosis unless pyelonephritis was also present.

Apparently, the pathologic factor necessary for the appearance of hypertension is inflammatory disease of the vessels, and such lesions as acute arteritis, arteriolitis, productive endarteritis and necrotizing arteriolitis, together with hyperplastic arteriosclerosis, were commonly noted in the cases studied. In the cases in which hypertension was present it did not differ from that of essential hypertension without demonstrable clinical disease of the kidneys.

Whether the changes in the arterioles of the kidneys result from primary disease of the kidneys or primary angiospasm of undetermined origin, the result is the same. If the spasm is persistent, organic changes in the arterioles occur and hypertension is persistent. If the endo-

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132. Blackman, S. S., Jr.: Arteriosclerosis and Partial Obstruction of the Main Renal Arteries in Association with "Essential" Hypertension in Man, Bull. Johns Hopkins Hosp. **65**:353 (Nov.) 1939. Mulholland, S. W.: Hypertension's Challenge to Urology, J. Urol. **42**:957 (Dec.) 1939. Nesbit, R. M., and Ratliff, R. K.: Hypertension Associated with Unilateral Nephropathy, ibid. **43**:427 (March) 1940. MacKenzie, D. W., and Seng, M. I.: Urological Aspects of Hypertension, Surg., Gynec. & Obst. **70**:578 (Feb., no. 2 A) 1940. Maher, C. C., and Mosika, P. H.: Urologic Hypertension, J. Urol. **41**:893 (June) 1939. Blackman, S. S., Jr.: Arteriosclerosis and Partial Obstruction of the Main Renal Arteries in Association with "Essential" Hypertension in Man, Bull. Johns Hopkins Hosp. **65**:353 (Nov.) 1939. Stewart, C. F.: Arteriosclerosis of the Renal Artery Orifices with Severe Hypertension, J. A. M. A. **114**:2099 (May 25) 1940.

133. Weiss, S., and Parker, F., Jr.: Pyelonephritis: Its Relation to Vascular Lesions and to Arterial Hypertension, Medicine **18**:221 (Sept.) 1939.

thelium becomes proliferative and necrosis occurs, the disease pursues a malignant course.

Page[134] reported another method for the induction of arterial hypertension experimentally in animals. This is accomplished by the production of severe fibrocollagenous perinephritis, through wrapping the kidney in cellophane. By this method the renal pedicle is left free, and renal ischemia is produced by the constricting perirenal fibrosis, which affects the structure of the kidney directly. Removal of such a kidney, if the other kidney is normal, abolishes the hypertension. Denervation of the renal pedicle does not prevent the development of hypertension. Bilateral removal of the adrenal glands abolishes the increase in pressure, but slight hypertension persists if the animals are treated with adequate amounts of sodium chloride and renal cortical extract. This indicates that perinephritis may be a factor in the production of hypertension in man.

Page[135] also demonstrated that constriction of the aorta may produce hypertension in dogs if the constriction is above the level of the renal arteries; if below, hypertension does not occur. It was noted that to secure such a rise in blood pressure, the aorta must be constricted just above the renal arteries. This is in agreement with work previously reported. If, however, the aorta is constricted or occluded at the arch of the aorta, near the site of constriction which is present in human coarctation, hypertension does not develop. There is some reduction in pressure distal to the occlusion, with a tendency to return to normal later. After several days the pressure in the femoral artery may fall progressively without reduction of pressure in the carotid artery. The failure to produce persistent hypertension under these conditions is attributed to the fact that in dogs an extensive collateral circulation readily develops. If the constriction is made within a short distance below the origin of the renal vessels and the aorta is occluded or constricted at the level of the diaphragm, hypertension occurs. Removal of the kidneys reduces or abolishes hypertension. Page expressed the opinion that these experiments suggest that the hypertension which occurs in coarctation of the human aorta is actually of renal origin.

Another method[136] for the production of hypertension by the prevention of renal hypertrophy was described by Greenwood, Nassim and Taylor.

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134. Page, I. H.: Production of Arterial Hypertension by Cellophane Perinephritis, J. A. M. A. **113**:2046 (Dec. 2) 1939.

135. Page, I. H.: The Effect of Chronic Constriction of the Aorta on the Arterial Blood Pressure in Dogs: An Attempt to Produce Coarctation of the Aorta, Am. Heart J. **19**:218 (Feb.) 1940.

136. Greenwood, W. F.; Nassim, R., and Taylor, N. V.: The Production of Hypertension by the Prevention of Kidney Hypertrophy, Canad. M. A. J. **41**: 443 (Nov.) 1939.

Short and Johnson,[137] in studying the relation of overweight to blood pressure, expressed the opinion that as a factor in hypertension overweight has been regarded as more important than it actually is. This they concluded in spite of their observation that the incidence of hypertension in a large group of overweight persons seemed to be increased, but to a less degree than that reported by others. The increase seemed to be more evident in the diastolic than in the systolic readings.

In contrast to this, Wood and Cash[138] found in dogs with experimental hypertension that the systolic pressure rose with gain in weight and declined with loss in weight. The diastolic pressure varied but little. They expressed the belief that overweight may be a factor of some importance in elevation of the systolic pressure.

It would seem that comparison of these results with those in man is hardly justifiable.

De Wesselow and Thomson[139] studied the serum electrolytes, particularly sodium, potassium and calcium, in cases of hypertension. It was found that changes in the diet intake of these substances had little or no effect on the variations in blood pressure in either normal or hypertensive persons. Large quantities of sodium seemed to result in a rise in blood pressure, while very large amounts of potassium caused a fall. These effects seem to be best explained by changes in blood volume and the effect of potassium in large amounts on the heart.

It appears that these salts are important in the regulation of pressure in Addison's disease or other disorders of the adrenal glands. When these structures are intact but little effect is noted in the blood pressure level, even when fairly large amounts of the salts are administered.

A CRITICAL REVIEW OF THE SURGICAL TREATMENT

BY DR. de TAKÁTS AND DR. BECK

This year's library output represents a consolidation and extension of the achievements of previous years; hence reviews of monographs and symposiums dominate the field. The articles selected for review are those which contain material of interest for the nonsurgical reader.

137. Short, J. J., and Johnson, H. J.: An Evaluation of the Influence of Overweight on Blood Pressures of Healthy Men: A Study of 3,516 Individuals Applying for Periodic Health Examinations, Am. J. M. Sc. **198**:220 (Aug.) 1939.

138. Wood, E. J., Jr., and Cash, J. R.: Obesity and Hypertension: Clinical and Experimental Observations, Ann. Int. Med. **13**:81 (July) 1939.

139. de Wesselow, O. L. V. S., and Thomson, W. A. R.: Study of the Serum Electrolytes in Hypertension, Quart. J. Med. **8**:361 (Oct.) 1939.

PARAVERTEBRAL BLOCK

The injection of procaine or alcohol into the region of the ganglionated trunk of the sympathetic nervous system is still gaining in favor. In his thought-provoking monograph on the surgery of pain, which has recently been translated, Leriche [140] summarized many years of clinical research on the diagnostic and therapeutic value of the abolition of pain by injections of procaine into the sympathetic ganglions. These have been carried out in cases of facial neuralgia that is not trigeminal, of post-traumatic spreading neuralgia, of causalgia in painful amputation stumps, of pain due to vasoconstriction, of angina pectoris and of various types of visceral pain. The critical reader may find a few gaps in the author's marshaled evidence, but there can be no doubt about the profound influence he has exerted on the surgery of the autonomic nervous system and on efforts to control pain.

In last year's review we noted the emphasis of Ochsner and DeBakey on the importance of vasospasm as a readily controllable factor in the prognosis and treatment of peripheral vascular disease. In a critical survey [141] they drew attention to the relative ease and safety with which injections can be made in paravertebral ganglions, even in outpatient clinics. Their treatment of 22 patients with thrombophlebitis by procaine block is described and illustrated in an article [142] in which conservative and radical methods of prophylaxis are discussed. Equally impressed with the frequency and importance of vasospastic states was Homans,[1] who in his recent classic monograph on circulatory diseases of the extremities devoted considerable space to the discussion of the technic and results of paravertebral injections.

Collens and Wilensky [3] and Samuels [143] took a different view of vasospasm and did not place its release in the center of therapeutic aims. It may well be that the intermittent venous hyperemia induced by the former and the hypertonic solution of sodium chloride employed by the latter obtain the same objective, but by different routes. As Ochsner and DeBakey [141] pointed out, "the paravertebral block is actually the more conservative procedure, because the patient may be completely relieved from vasospasm in a few minutes and thus the

140. Leriche, R.: The Surgery of Pain, translated and edited by A. Young, Baltimore, Williams & Wilkins Company, 1939.

141. Ochsner, A., and DeBakey, M.: Peripheral Vascular Disease: A Critical Survey of Its Conservative and Radical Treatment, Surg., Gynec. & Obst. **70:** 1058 (June) 1940.

142. Ochsner, A., and DeBakey, M.: Therapy of Phlebothrombosis and Thrombophlebitis, Arch. Surg. **40:**208 (Feb.) 1940.

143. Samuels, S. S.: The Diagnosis and Treatment of Diseases of the Peripheral Arteries, ed. 2, New York, Oxford University Press, 1940.

patient is saved the loss of time and expense required by the prolonged therapy of vascular exercises."

There really need be no conflict between these methods; in our experience[144] the intermittent venous hyperemia which gradually increases the capacity of the venocapillary bed may be carried out in the home by a simple, inexpensive apparatus; it acts much better in a limb the sympathetic vasoconstrictors of which have been previously blocked. But the paravertebral block is safe and effective only in the hands of those who can visualize the structures to be passed by the needle; surgical experience with exposure of the ganglionated trunk is of great help in the performance of this chemical block. As Homans[1] stated: "The operator must have the ability to visualize the spinal column, its transverse processes and the ribs and to know where the point of his needle is going. Above all he must have the disposition suited to local anesthesia, the gentleness, deliberation and power of assurance without which injections of procaine are a trial to the patient, in some cases, an agony."

A valuable suggestion by Gage[145] is the use of sympathetic block before the surgical attack on an aneurysm. For the lower extremity a paravertebral block with alcohol was advised, while for the upper extremity preoperative and postoperative infiltrations of procaine into the stellate ganglion were suggested. Among 15 patients so treated not a single case of gangrene developed. Sympathetic block aids the development of an efficient collateral circulation, increases the total blood flow to the extremity and prevents postoperative spasm. The aneurysmal sac may decrease, and intrasaccular clotting can occur.

SURGICAL TREATMENT OF VENOUS THROMBOSIS

During the last few years certain principles have crystallized the wider adoption of which might shorten convalescence, diminish permanent edema and lessen the danger of pulmonary embolism. The occurrence of vasospasm, resulting in pain and edema, has already been mentioned and its release by paravertebral block described.[142] The ligation of the femoral vein proximal to a septic thrombus, followed by a prompt drop in the pulse rate and the temperature to normal, has been discussed in previous reviews and another instance cited by Oschsner and DeBakey.[142] Taylor[146] tied the external iliac vein in a

144. de Takáts, G.; Beck, W. C., and Roth, E. A.: The Neurocirculatory Clinic: I. Peripheral Vascular Disease, Ann. Int. Med. **13**:957 (Dec.) 1939.

145. Gage, M.: The Development of Collateral Circulation in Peripheral Aneurysms by Sympathetic Block, editorial, Surgery **7**:792 (May) 1940.

146. Taylor, K. P. A.: Pulmonary Emboli Following Injection of Varicose Vein: Control by Ligation of External Iliac Vein, Am. J. Surg. **45**:145 (July) 1939.

patient who had a pulmonary infarct following the injection of varicose veins. The extraction of a bland, nonseptic thrombus from the femoral vein through an opening in the saphenous vein has been reported.[147] Homans [1] called attention to a treacherous, often unrecognized, site of thrombosis in the deep veins of the lower part of the leg involving the posterior tibial, anterior tibial or peroneal system. Because there are many of these veins, little or no sign of venous stasis occurs. If elevation for ten days does not result in complete disappearance of soreness, swelling or cyanosis, Homans advocated the division of the femoral vein below the renal profundae. In his experience, cyanosis or edema after the procedure is slight, if present at all.

This type of thrombosis, as Homans emphasized, is so dangerous that the division of the femoral vein should not be unduly delayed. Of 4 such patients seen recently by one of us (G. de T.), 3 had massive pulmonary infarcts and 2 died. The typical phlegmasia alba dolens, "the iliofemoral thrombophlebitis," however, carries only a slight incidence of pulmonary embolism,[147] and it is much more difficult to decide on surgical intervention in such cases. More than two massive pulmonary infarcts, however, call for a proximal division of the vein; this must be made at the level of the common iliac vein to exclude the hypogastric bed from releasing emboli. Possibly the wider application of heparin will increasingly restrict the indication for proximal venous ligation.

HEPARIN IN THE SURGICAL TREATMENT OF BLOOD VESSELS

Murray [102a] has recently given the latest experiences of the Toronto group with the intravenous injection of purified heparin in treatment of vascular diseases. To date his group has given preventive treatment to 440 patients in the hospital, in none of whom thrombosis and embolism occurred. Patients with thrombophlebitis were thought to be definitely improved by the treatment; within a few hours after administration pain diminished and the temperature had begun to fall. Murray gained the impression that there has been less persistent edema in the treated than in the control group. While pulmonary embolism occurred in 15 per cent of 300 control subjects, it did not occur in 91 patients to whom heparin was given. Patients with migrating phlebitis, however, did not respond so well.

Twenty-nine patients with pulmonary embolism were treated; none of these died. The dyspnea and other signs improved rapidly, and within twenty-four hours the patients seemed definitely on the road to

147. de Takáts, G., and Jesser, J. H.: Pulmonary Embolism: Suggestions for Its Diagnosis, Prevention and Management, J. A. M. A. **114**:1415 (April 13) 1940.

recovery. Some of the patients were of the type for which prognosis seemed extremely bad.

Peripheral arterial embolectomy was successful in 12 cases in which heparin was used. Heparin was injected into the vessel at the site of operation, and the injection was continued intravenously for from three to fourteen days. In 1 case a venous graft was placed in an artery, which remained patent. In 6 cases of mesenteric thrombosis in which extensive resections of the bowel were required heparin was given. Four of the patients lived; 1 died of bronchopneumonia and 1 of peritonitis. Eight splenectomized patients were given heparin, as it is known that portal thrombosis is a definite factor in mortality. In none did thrombosis develop.

McClure and Lam [148] reported their experience in use of heparin in 11 cases. Eight of the patients had pulmonary embolism, and all recovered. One patient with popliteal embolism and 1 with arterial thrombosis received heparin. The authors pointed out that considerable variation in the amount of heparin is necessary to prolong the clotting time to an optimum level.

As stated in our last review, the clinical use of purified heparin is one of the far reaching contributions to vascular surgery. The price still prohibits its general application for prolonged periods. Until a cheaper product or a new synthetic drug becomes available, one may have to resort to shorter periods of application or to substitution with leeches. The treatment of thrombophlebitis with leeches was revived by Termier (cited by Page [135]) in 1922. Mahorner and Ochsner [149] summarized the extensive bibliography up to 1933 and reported several cases of their own. Ochsner still employs the method in treatment of portal thrombophlebitis.[142] As some reports have indicated, however, that embolism may be favored during its application, the procedure must be used with caution. In our own experience, leeches slightly prolong systemic coagulation time and seem to hasten the disappearance of edema. Purified hirudin might be more advantageous than the cumbersome use of leeches, which may produce infection. Another substitute for heparin may be some inorganic solutions of sulfur, such as sodium thiosulfate or sodium tetrathionate, which in the experience of Theis and Freeland [30] are useful in relief of thrombotic and vasospastic states and which have been found to increase the glutathione content of the liver and blood. Glutathione is a catalyst of oxidation which activates inactive oxyhemoglobin. Its relation to the clotting phenomenon is yet

148. McClure, R. D., and Lam, C. R.: Experiences in Heparin Administration, J. A. M. A. **114**:2085 (May 25) 1940.

149. Mahorner, H. R., and Ochsner, A.: The Use of Leeches in the Treatment of Phlebitis and the Prevention of Postoperative Embolism, Ann. Surg. **98**:408 (Sept.) 1933.

unclear; clinically, however, rapid regression of attacks of thrombophlebitis, expecially of the migrating type, has been observed by one of us (G. de T.). It has been suggested that the injection of the sulfur compounds actually mobilizes the patient's own heparin.[150]

ANEURYSMS AND ANGIOMAS

A number of interesting case reports[151] reveal the difficulties of management, especially in cases of the congenital variety. The cavernous hemangioma in Matas' case recurred eleven years after disarticulation of the shoulder. The only new principle introduced in this technically difficult field is the employment of sympathetic paralysis, temporary or permanent, before the radical attack on the aneurysm is undertaken; this procedure facilitates the development of collateral circulation to such an extent that ligations and excisions can be undertaken with more safety. It also seems to facilitate spontaneous thrombosis in the aneurysmal sacs by decreasing peripheral resistance.[152]

CERVICAL RIB AND THE SCALENUS SYNDROME

Two papers containing a total of 41 new cases of this syndrome have recently been presented at a meeting of the Southern Surgical Association by Donald and Morton[153] and by Aylesworth.[154] The recognition of symptoms due to the compression of the brachial plexus and the subclavian artery by the scalenus anterior muscle has increased in frequency in the last few years, even though Murphy as early as 1906 drew attention to the possible role of the scalenus anterior muscle in the production of symptoms arising from cervical ribs. In 16 of the 21 cases reported by Donald and Morton, the disturbance was not associated with a cervical rib. Trauma, occupational strain and improper posture precipitated the symptoms. The results following the section of the scalenus muscle were excellent. In 14 of the cases there was complete relief; in only 2 did symptoms recur. Many mild conditions respond to conservative therapy and need no operation. Aylesworth emphasized trauma as an etiologic factor in 80 per cent of 20 cases. In 12 cases

150. Bancroft, F. R., in discussion on Murray, G. D. W., and Best, C. H.: The Use of Heparin in Thrombosis, Ann. Surg. **108**:173 (Aug.) 1938.

151. Matas, R.: Congenital Arteriovenous Angioma of the Arm: Metastasis Eleven Years After Amputation, Ann. Surg. **111**:1021 (June) 1940. Gatch, W. D.: Case of Large False Aneurysm of the Right Subclavian Artery Successfully Treated by a Modification of the Matas Operation, ibid. **111**:1046 (June) 1940.

152. Discussion on papers of Matas and Gatch, Ann. Surg. **111**:1052 (June) 1940. Discussion on Gage.[145]

153. Donald, J. M., and Morton, B. F.: The Scalenus Anticus Syndrome With and Without Cervical Rib, Ann. Surg. **111**:709 (May) 1940.

154. Aylesworth, K. H.: The Cervicobrachial Syndrome: A Discussion of the Etiology with Report of Twenty Cases, Ann. Surg. **111**:724 (May) 1940.

operation was performed with satisfactory results, except in 1 case in which the condition was unsuitable for tenotomy. In order to simplify the nomenclature and to express a more correct symptomatology, he suggested the term "cervicobrachial syndrome."

In a thoughtful discussion, Patterson [155] enumerated many pitfalls which may beset those who regard any pain in the arm or shoulder as due to compression by the scalenus muscle. It has been our custom to make a diagnosis by exclusion. Subdeltoid bursitis, arthritis of the shoulder, cervicodorsal arthritis of the spine, tuberculous lymph glands of the neck, apical tuberculosis with adhesive pleurisy at the first rib and other conditions have been observed to simulate this syndrome. It may, of course, be argued that all these conditions are capable of producing reflex spasm in the scalenus anterior muscle. If this is present the diagnostic test of Gage,[156] in which the scalenus muscle is infiltrated with procaine, will reveal it. Nevertheless, by elimination of the source the muscle spasm often relaxes. While the success is dramatic, when carried out in the properly selected case, it is to be expected that in a number of cases tenotomy is unnecessary and will yield no results. It is important to prevent regeneration by excision of a segment of muscle and to treat the chronic brachial neuritis with rest and thiamine chloride after the operation.

SYMPATHECTOMY IN TREATMENT OF PERIPHERAL VASCULAR DISEASE

Smithwick,[157] in a continuation of his studies, stated that the arguments for and against sympathetic ganglionectomy in the treatment of peripheral vascular disease emphasize the importance of complete denervation by a preganglionic procedure. In his operation he divides the sympathetic trunk below the third dorsal ganglion and resects the second and third intercostal nerves, following them to their anterior and posterior roots. The posterior roots are divided just proximal to its ganglion. This results in satisfactory denervation of the upper extremity. For sympathetic denervation of the lower extremity the second and third lumbar ganglions and their rami are excised. Interesting and characteristic changes take place after preganglionic sympathectomy. For the first few days after operation the extremity is dry, warm and of excellent color. Reflex sweat and vasomotor activities are abolished. Between the third and the fifth day a sudden burst of sympathetic activity

155. Patterson, R. H.: Cervical Ribs and the Scalenus Muscle Syndrome, Ann. Surg. **111**:531 (April) 1940.

156. Gage, M.: Scalenus Anticus Syndrome: A Diagnostic and Confirmatory Test, Surgery **5**:599 (April) 1939.

157. Smithwick, R. M.: Surgical Intervention on the Sympathetic Nervous System for Peripheral Vascular Disease, Arch. Surg. **40**:286 (Feb.) 1940.

takes place. The extremity begins to perspire, becomes cooler and is often discolored. This is interpreted as a spontaneous outflow of impulses from the decentralized sympathetic ganglions. Actually, we have never seen the phenomena when the ganglions were also removed, except immediately after the operation. During the second and third weeks the surface temperature gradually falls until it reaches a stable level. Sensitivity to epinephrine appears and is probably largely due to the fall in surface temperature. Months or years after operation a well sympathectomized extremity should have a high surface temperature with little or no rise on blocking with procaine hydrochloride. There is complete abolition of reflex vasomotor and sweating responses.

When the operation is incomplete the surface temperature is only slightly elevated, or not at all. Peripheral nerve block results in a marked rise in cutaneous temperature. Reflex sweating and vasomotor responses are present. Sensitivity to epinephrine will not appear.

From six months to a year and a half after what is thought to be a complete operation a "relapse" may take place. The situation is undoubtedly due to partial regeneration of sympathetic fibers. Smithwick found that the vasomotor reflex was absent in all of the 8 cases in which relapse occurred, but that reflex sweating was present. While vasomotor responses were determined with the help of a photoelectric cell, the sweat responses were studied by measuring cutaneous resistance and the psychogalvanic reflex. The significance of the findings is not clear.

The clinical results depend, in addition to the completeness of preganglionic denervation, on the degree of local fault in the vessels. Results have been excellent in the early stages. When there are sclerodermatous changes calcification of tissues or destruction of bone, the results are inferior. These observations confirm those of Patterson Ross, which have been reviewed in former years.

In thromboangiitis obliterans the addition of sympathectomy to the nerve crushing and minor amputations previously employed has markedly decreased the percentage of major amputations; this is especially true when the popliteal artery is patent. While, obviously, the most brilliant results are obtained in cases of purely vasospastic disorders, worth while improvement may often follow in cases in which both organic obstruction and spasm of arteries are known to exist.

The degree of structural involvement, the technic of operation and the preoperative diagnosis were the three factors in an analysis of the percentage of failures.[158] A method of extended cervical sympathectomy has been described in which the intermediate ganglion, the vertebral

158. de Takáts, G.: Analysis of Results Following Sympathectomy for Peripheral Vascular Disease, Am. J. Surg. **47**:78 (Jan.) 1940.

plexus and the ganglionated dorsal chain from the stellate to below the third thoracic ganglion have been excised in 21 cases to date, with results that in our hands are equal, if not superior, to the preganglionic sections. The importance of the first white ramus in supplying vasomotor fibers to the upper extremity has not yet been definitely established. A satisfactory number of cases in which the preganglionic type of operation is done on one side and the extended cervicodorsal sympathectomy on the other should settle this technical question.

The post-traumatic dystrophy of extremities, which is such a stumbling block to medicolegal experts, has been studied by Haldbo,[159] who expressed the belief that the severe forms resisting conservative therapy should be treated by sympathetic denervation.

Ochsner and DeBakey [141] gave a complete review of the various approaches to the cervicodorsal and lumbar sympathetic trunks, together with the history of their development. The new and little known approach of Leriche, Percira and DeBakey [160] was again described. In addition to excluding neurogenic impulses to the lower extremity, they employ section of the splanchnic nerve to decrease the reflex secretion of epinephrine, which may play a role in vasospastic states of the extremities. Our experience with this approach, to which occasionally resection of the tip of the twelfth rib may be added, has been favorable.

EMBOLECTOMY

The valuable addition of heparin in the postoperative care of patients who have had arterial sutures has already been discussed.[102a] Haimovici [161] assembled in a small practical monograph the clinical applications of recent research on acute arterial occlusions. He pointed out that the embolus sets up a reaction of the vessel wall within the first ten to twelve hours, which again stimulates extension of the thrombosis. The intimal lesion, thus produced, is responsible for secondary thrombosis after the extraction of the clot; the adventitial reaction is the starting point of vasoconstrictor reflexes which affect the main vessel and its collaterals. The extension of thrombosis blocks a number of collaterals, the patency of which might save the limb from gangrene. Embolectomy is therefore urged within the first ten to twelve hours following the vascular accident if known conservative measures fail. If this period

159. Haldbo, H.: Post-Traumatic Dystrophy of Extremities, Nord. med. **3**: 2053 (July 8) 1939.

160. Leriche, R.; Percira, S., and DeBakey, M.: La résection des nerfs splanchniques. Technique et résultats de quelques observations de thromboangiite oblitérant, hypertension paroxystique, mégacolon et dolichocholon, Méd. Contemp., July 1937, no. 27.

161. Haimovici, H.: Les occlusions artérielles des membres, Paris, Masson & Cie, 1939.

has been missed, arteriectomy (see our previous reviews) is advocated; if this should fail to improve the circulation, lumbar sympathectomy by procaine block or surgical excision is in order.

It may seem like overzealous activity to perform multiple operations on a patient whose cardiovascular system is crippled by a myocardial thrombus, a mitral stenosis with vegetations or ulcerating endocarditis. Nevertheless, this seems justifiable if a patient's leg can be saved from amputation. The indifference of physicians to a situation of the utmost urgency in cases of acute arterial occlusion can be overcome only by the demonstration of the dramatic results which may be obtained by an early and skilful attack on the occluded artery. It is true that roughly 50 per cent of arterial emboli do not lead to gangrene, but these can be readily recognized in the first few hours by their favorable response to physical and drug therapy.

SURGICAL TREATMENT OF HYPERTENSION

Progress in the surgical therapy of hypertension is continuing from several sources. Better understanding and clearer classification of this syndrome have been brought about by the studies of Schroeder and Steele,[108] who classified 218 cases as those of renal, neurogenic, endocrine, vascular and unclassified origin. The surgeon will greatly benefit from a better understanding of the nature of the hypertension with which he is dealing. The point should be made that not in all cases is the hypertension due to the presence of Goldblatt kidneys.

A report of the effect of supradiaphragmatic section of the splanchnic nerves has been made by Braden and Kahn.[162] In a review of 264 cases of Peet's series in which the patients were followed from six months to five years, they found an operative mortality of 3 per cent and a postoperative mortality rate of 23 per cent. In 43 per cent of the patients with recurrence the blood pressure was significantly reduced; 84 per cent were able to return to their former activities, and 87 per cent had symptomatic relief. In their experience selection of cases is not possible with the present methods.

Adson,[163] on the other hand, discussed his experience with subdiaphragmatic splanchnic resection. He used the depressor effect of sedatives and the cold pressor test as valuable guides in selecting patients for operation. Of an unselected group of 156 patients, 1 died, 20 per cent recovered normal blood pressure and 35 per cent obtained marked reduction in pressure. No effect on blood pressure was obtained in 20

162. Braden, S., and Kahn, E. A.: Surgical Treatment of Hypertension: Preliminary Report of Study and Results in Two Hundred and Sixty-Four Cases, Yale J. Biol. & Med. **11**:449 (May) 1939.

163. Adson, A. W.: Classification of Hypertension: Prognosis and Management, Mil. Surgeon **84**:537 (June) 1939.

per cent, and temporary lowering was found in 25 per cent. Symptomatic relief was obtained in 85 to 95 per cent of the two groups showing favorable responses.

It is remarkable that two surgeons using different technical approaches and different selections of cases should have such similar results. Roughly 50 per cent of the patients had objective evidence of improvement, whereas 85 per cent reported marked symptomatic relief.

Davis and Barker [164] found that approximately 50 per cent of their hypertensive patients showed both objective and symptomatic relief after sulfocyanate therapy. After a good initial response, 25 per cent of the patients became refractory, and much larger doses were required to maintain a satisfactory cyanate level. In the remaining group a gradual rise in blood pressure occurred, in spite of a constantly maintained and seemingly adequate concentration of cyanate in the blood. The authors considered only surgical treatment for patients who were resistant to cyanates and reported 6 cases of this type. In these cases bilateral supradiaphragmatic splanchnic section alone failed to decrease the blood pressure or to alter the chemical constituents of the blood. In such cases, however, they could obtain a satisfactory response to cyanates, which was not possible before the operation. They did not attempt to explain this acquired sensitivity, although possible reasons were suggested.

Smithwick,[165] in his recent report based on experience with approximately 150 patients suffering from hypertension, established the following criteria for successful sympathectomy: The operation must be complete; it should be preganglionic in type and extensive enough to guard against future regeneration. He described an operation which removes the entire splanchnic nerve from its roots to its entrance into the celiac ganglion, divides all its branches to the aorta and excises the ganglionated trunk with the communicating rami of the ninth dorsal to the second lumbar nerve, inclusive. This seems to be the minimal procedure which consistently produces the characteristic postural hypotension that the author establishes as a criterion of successful splanchnic denervation. With this standardized technical procedure he has now attacked different stages of the disease, which division is largely based on changes in the eyegrounds. The less advanced stages have shown far better response than the more advanced ones.

The operation of Smithwick is preganglionic in type; it is so extensive that individual variations, for which the sympathetic nervous system

164. Davis, L., and Barker, M. H.: Clinical and Experimental Experiences in the Surgical Treatment of Hypertension, Ann. Surg. **110**:1016 (Dec.) 1939.

165. Smithwick, R. H.: A Technique for Splanchnic Resection for Hypertension, Surgery **7**:1 (Jan.) 1940.

is notorious, will not result in escape from section; moreover, regeneration over such a wide area is not to be expected. For the first time, we believe, a method of total splanchnic nerve section has been presented; this may explain many of the failures in previous series. The factor of the stage of the disease has also been taken in account, with the help of which it may reasonably be possible to predict the results of operation in the individual case. Smithwick's work will undoubtedly give new impetus along this line of clinical research.

Ascroft [166] recommended splanchnic resection only when the hypertension is labile and of short duration; even then, he stated that the results are unpredictable. He suggested nephro-omentopexy, in addition to sympathectomy, as a means of increasing renal arterial supply.

Because of the beneficial effects of collateral circulation on the experimental hypertension produced by renal ischemia, nephro-omentopexy was suggested in treatment of human subjects and was carried out, in the first case four years ago.[167] The patient is still alive, and since that time 4 others have been subjected to decapsulation and scarification of the kidney, which was then wrapped up in omentum or muscle flaps. Bruger and Carter,[168] in a preliminary note, reported 8 cases in which nephro-omentoplexy was undertaken on the right kidney in man. In 1 case, in which autopsy was later performed, they were able to demonstrate particles of india ink in the omentum when the kidney was perfused through the renal artery. However, from their histologic sections only venous drainage of the kidney into the omentum could be demonstrated. Only prolonged observations will decide the merits of this procedure. It seems that simple decapsulation will not bring about any increase in circulation [169] and that incisions into the cortex followed by omental or muscular implants must be made to facilitate vascular connections.

AMPUTATIONS

Williams and O'Kane [170] presented a simple classification of gangrene of the extremities in patients with diabetes: They are vascular, inflammatory and mixed. The degree in which the vascular and the inflammatory component is present will decide the therapy employed.

166. Ascroft, P. B.: The Surgical Treatment of Arterial Hypertension, Lancet **2**:113 (July 15) 1939.

167. de Takáts, G.: Revascularization of the Nephrosclerotic Kidney, Proc. Central Soc. Clin. Research, 1939, p. 49.

168. Bruger, M., and Carter, R. F.: Evidence of Communication Between Renal and Omental Blood Vessels Following Nephro-Omentopexy for Arterial Hypertension in Men: Preliminary Note, Am. J. M. Sc. **197**:832 (June) 1939.

169. Goldberg, S.; Rodbard, S., and Katz, L. N.: Increased Collateral Blood Supply to the Kidney in Renal Hypertension, Surgery **7**:869 (June) 1940.

170. Williams, F. W., and O'Kane, T. J.: Clinical Classification of Lesions of Lower Extremities Associated with Diabetes, Arch. Surg. **40**:685 (April) 1940.

Faxon [171] reported on 204 unilateral and 58 bilateral amputations done in 530 cases of obliterative vascular disease. In 52 instances the patients were seriously ill and a guillotine amputation was done; three weeks later reamputation was performed in 84 per cent of the surviving patients. A primary closed amputation was done in 40 per cent of the cases. In amputations for Buerger's disease amputation below the knee was usually unsuccessful, even in the presence of a pulsating popliteal artery; in 75 per cent reamputation was necessary. The Gritti-Stokes amputation is preferred, and this can be done even in the absence of a popliteal pulse. The circular, inverted, funnel-shaped amputation just above the patella, however, gave the least postoperative reaction and is thus the safest for feeble patients.

In a report of the largest series of amputations for diabetic gangrene ever reported, McKittrick [172] described the organization at the New England Deaconess Hospital for the care of patients with diabetes mellitus and gangrene and discussed 972 cases of diabetic vascular deficiency. The mortality in the hospital was 9.4 per cent. The mortality after major amputations was 13.9 per cent. Bilateral amputations were done in 16 per cent of the cases. The mortality after the second amputation was definitely lower than that after the first. The causes of death in 73 cases were: infection, 40 per cent; cardiorenal diseases, 40 per cent, and pulmonary complications, 18 per cent, in half of which the condition was due to embolism. Patients who accepted bilateral amputation may look forward to nearly twice the life expectancy of those who had only one leg amputated. Of 33 patients who refused amputation, 11 patients survived later amputation; 20 died either of progressive gangrene or after amputation elsewhere; 1 had slow healing, but could never walk on his foot, and 1 died of coronary thrombosis four years after an amputation.

Taylor [173] reported on 113 amputations, with a case mortality of 37.6 per cent. Forty-six of the deaths were due to infected stumps; in 63 per cent of the survivors stump necrosis and suppuration were noted. This situation was markedly improved by omitting the suture of fascia entirely and suturing the skin only loosely.

Reynolds and one of us (G. de T.) [174] described the determination of the level of amputation with the help of cutaneous temperatures and

171. Faxon, H. A.: Major Amputations for Peripheral Arterial Obliterative Disease, J. A. M. A. **113**:1199 (Sept. 23) 1939.

172. McKittrick, L. S.: Diabetic Gangrene: Review of Nine Hundred and Seventy-Two Cases, Arch. Surg. **40**:352 (Feb.) 1940.

173. Taylor, F. W.: Arteriosclerotic Gangrene, J. A. M. A. **113**:1196 (Sept. 23) 1939.

174. de Takáts, G., and Reynolds, J. T.: Amputation for Peripheral Vascular Disease, Arch. Surg. **40**:253 (Feb.) 1940.

histamine flares. The mortality of 33 per cent was decreased to 7.6 per cent by the prophylactic use of antianaerobic serum and by the adoption of the Callander amputation through the knee joint; 16 of the 20 patients who had Callander amputations were able to wear an artificial limb. The amount of expense and suffering caused by unnecessary delay of unavoidable amputations was discussed. When amputation was done before infection supervened the mortality was markedly lowered.

Although little difficulty was experienced with painful amputation stumps by some of the authors, notably by McKittrick,[172] a number of articles have been devoted to the management of this syndrome. We believe that the best treatment is prophylactic. The large nerves should be crushed and ligated or cauterized and no injections of alcohol should be made into them; nor should they be traumatized in any way.[174] In a series of 250 amputations, Colonna and vom Saal[175] had to do 12 reamputations; they asserted that injection of alcohol into the nerve effectively prevents the formation of neuroma. Virall[176] also paid much attention to the painless stump and the weight-bearing ability. He advised against cutting the nerves short and injecting alcohol into them. Sliosberg[101] reported on 74 patients with painful amputation stumps who were treated with daily injections of 0.01 Gm. of vitamin B_1. Eleven were completely relieved, 39 markedly improved, 10 moderately improved and 7 only slightly benefited. The patients who were helped showed a favorable response after a few injections.

Gallinek[177] discussed the fantom limb. Stimuli applied to the stump are localized partly in the stump and partly in the nonexisting part. Pressing or stroking the stump may relieve this syndrome. The fantom limb seems smaller, although the patient has no definite idea of its aspect or color. The essential factor in producing this sensation is peripheral sensory stimulation; the fantom disappears simultaneously with the relief of pain. A cerebral factor, however, is important, and in the psychotic patient other symptoms are added which produce a type of hallucination.

In analyzing a series of amputations from the Charity Hospital in New Orleans, Veal[178] found that death in 24 of 67 cases was due to pulmonary complications. He expressed the opinion that in most of the cases of pneumonic origin the involvement was embolic. Postmortem

175. Colonna, P. C., and vom Saal, F.: Amputation Stumps of the Lower Extremities, J. A. M. A. **113**:997 (Sept. 9) 1939.

176. Virall, P. J.: Amputation Stumps and Artificial Limbs, Brit. M. J. **1**: 62 (Jan. 13) 1940.

177. Gallinek, A.: The Phantom Limb, Am. J. Psychiat. **96**:413, 1939.

178. Veal, J. R.: High Ligation of the Femoral Vein in Amputations of the Lower Extremity, J. A. M. A. **114**:1616 (April 27) 1940.

dissections revealed a clot in the stump of the femoral vein in all instances. Certain anatomic variations help the formation of a stagnation thrombus in a long venous stump. Therefore, in 29 consecutive cases he ligated the femoral vein below the saphenofemoral junction. None of the patients so treated had pulmonary complications.

This seems an important suggestion, as pulmonary emboli have caused a small but definite percentage of deaths in all the series reported. In many of the cases of infection, however, the venous periphlebitis may cause a matting together of the femoral artery and vein; the ligation of the latter becomes a delicate procedure.

In general, the lowering of mortality and the elimination of difficult weight bearing, with a better rehabilitation of the patient, are unmistakable trends in this field.

Book Reviews

Syphilis and Its Accomplices in Mischief: Society, the State and the Physician. By George M. Katsainos, M.D. Paper cover. 676 pages devoted to the above title, and 162 pages under the title of "Marriage and Syphilis.—A Treatis on Eugenics." Total price $5.00. Athens, Greece: Privately printed ("Kyklos" Publishing Company).

As the title might suggest, this is a rather unusual book. Its style is distinctly original and the volume is unique for its forceful bias and its decidedly prejudiced statements. It might be considered a philosophic essay rather than a technical treatise on a medicoethical subject. The author has gone to great lengths of erudition to distribute on a rather poorly organized framework citations from the Bible, early Greek mythology and the classics, as well as from the works of some of the better known syphilographers of the last decades. His book, therefore, becomes somewhat historical in character, but, unfortunately, it contains no bibliography. The following quotations may give a clearer insight into the style and character of the book:

> "Leprosy and syphilis are mirrors, in which man, beholding his reflection is covered with confusion and hides his face in terror, at the sight of his crimes. Leprosy and syphilis are the two terrible reagents, which, applied to man, prove him to be a sham, a counterfeit—false and untrue to himself. Leprosy and syphilis have shown men to be egotistical, selfish, narrow-minded and cowardly. Both these diseases have been, are at present, and will continue to be bugbears and phantasms, which ungrounded fear prevents man from grasping and strangling, or even feeling and becoming acquainted with their texture, much less of seeking out and finding the proper and appropriate means of prevention, since he is powerless to cure."
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> "But as the drugs by which syphilis is cured are potent chemical poisons, deadly in their effect and requiring the greatest care in their preparation, and even greater care in their application, the quacks have been ruled out of court and scientifically trained and certified physicians have undertaken to carry on their orgies. In view of such crimes as are committed on many syphilitic patients today one stands aghast at the number and the magnitude of their victims, and asks himself, "can such things be done by men of science?" Should one attempt to penetrate to the inner sanctuaries and mysteries of extortion and deceit committed today by physicians, he would be persuaded that in comparison with these, Polyphemus and the Lestrigonians, Pityocamptes and Procrustes—those bandits of old, would be exonerated and canonized as saints. Medicine needs to be purified; the house has fallen into decay and ruins; mouldy, worm-eaten, and infested with vermin, it needs being isolated with all that it contains and, like the house of Socrates in the "Clouds" of Aristophanes, be committed to the flames. Society and the state, the one limping the other blind, need a crutch. The laws which have hitherto governed us, remnants of the code of Moses, of Solon, of Lycurgus, of Numa, of Tribonianus, of Bacon, no less than of superstition, prejudice, fanaticism, and the unquestioned decrees of the great, need to be renovated. It is not enough that we would call to mind the sayings of the Nazarene "Put not new wine into old Bottles," we must put it into practice as well."

The author takes up the symptomatology and treatment of syphilis in a very superficial but decidedly prolix fashion. It is somewhat startling to have him discuss the use of arsphenamine (606) and of mercury (without mention of more recent and more popular drugs) as though they constituted all the modern armamentarium of antisyphilitic therapy. It might be of academic interest for the reader to reconsider, with the author, points of discussion on the treatment of

syphilis which were thought to have been settled years ago. In his "Conclusion" Katsainos states:

> "A disease, the very name of which is prudishly avoided by the lay press, and the victims of which society hates and condemns, the state prosecutes and punishes, and the medical profession deceives and plunders, and which is impossible to fight in the open, cannot be defeated, conquered, and consequently exterminated."

Although this book was evidently written for lay readers and is interesting because of its original presentation, it cannot be recommended to them because of its many generally unaccepted viewpoints. The physician will be disappointed in the book as a scientific work because of its inadequate consideration of the problem, particularly in the light of advances made during the last ten or fifteen years (a period which marks most of the progress in the treatment of syphilis from the social and medical point of view).

The section on "Marriage and Syphilis," which was written in 1922, is better organized. It covers much the same material as the first part, but there is more emphasis on heredosyphilis.

Provoked Alimentary Hyperglycemia: The Mechanism of the Tolerance Test. By Joseph Marshall Flint (from the Medical Clinic of the University of Lausanne, Prof. Dr. L. Michaud, Director). The Effect of the Macallum-Laughton Duodenal Extract upon Hypophyseal Diabetes. By Joseph Marshall Flint and Louis Michaud. Pp. 77. London, Ontario, Canada: A. B. Macallum, 1939.

This work, as indicated by the title, represents the report of two investigations by Dr. Flint, who formerly was a professor of surgery at Yale University. The author's summaries contain the following material:

"*Recapitulation.*—From studies on the intermediate carbohydrate metabolism by the angiostomy method, observations were selected that correspond to the ordinary tolerance test. These throw much light upon provoked alimentary hyperglycemia. A criss-cross or shift of function between the liver and intestine takes place at the beginning and end of the tolerance reaction by which they exchange roles as yielding and retaining organs vis-á-vis the blood sugar. This shift occurs in the following sequence: upon the appearance of carbohydrates in the duodenum, absorption of sugar begins and its concentration in the intestine mounts until it passes the retention point and is then yielded to the portal radicals. The increase in sugar concentration in the portal blood is the stimulus that induces a change of function in the liver. This reduces its yield to the zero point and then begins to retain sugar. In consequence, the liver remains during the entire period of the tolerance reaction a potent utilization and hypoglycemic factor as the sugar concentration mounts from the fasting level to the apex of the crochet and back to the initial level again. Retention by the organs and tissues during fasting and alimentary hyperglycemia forms the basis of utilization, the removal of sugar from the blood for the various purposes of the intermediate carbohydrate metabolism. Following the absorption of sugar from the intestine, a series of organic formulae occur that characterize the various phases of alimentary hyperglycemia. In the fasting state, the liver yield equals the combined organic and tissue retention; in the hyperglycemic phase of the tolerance test, the intestinal yield is greater than retention thus increasing the sugar concentration of the blood until at the apex of the reaction (circa 60 minutes)—its maximum concentration—a momentary balance is established when the yield is exactly equalled by retention. From this point, the formula changes—organic and tissue retention exceeds the yield—and so the hypoglycemic phase of alimentary hyperglycemia is inaugurated. This leads to a gradually diminishing sugar concentration until, as the initial level is approached, the intestine-liver criss-cross recurs in a reverse sense and the original fasting formula is restored. It is evident that alimentary hyperglycemia is a resorption phenomenon between the intestine and the organs controlled and equalized by the glycoregulatory mechanism. Unusual tolerance reactions such as those obtained from different regimes, fasting, constitutional factors, etc., are to be explained on the basis of changes induced by the endocrine sugar control. Similarly, diabetic

tolerance tests are exaggerations of these same factors due to derangements in regulation that vary in degree with the type and severity of the disease. A study of the control will elucidate the possibilities and their effect on the tolerance reaction. In a large sense, defects in the sugar control also indicate the type of diabetes. Overproduction of the anterior pituitary incretions cause hypophyseal diabetes; underproduction of the pancreatic elements lead to pancreatic diabetes; and overproduction of the pancreatic incretions is followed by hyperinsulinism. These are now obvious and self evident consequences of disturbances of the glycoregulatory system.

"Normally, the function of the Macallum-Laughton extract, derived from the duodenum and pancreas, is (a) to stabilize and maintain the blood sugar level, (b) to synergise the action of insulin, (c) to overcome insulin resistance, (d) to improve the utilization by removing sugar from the blood for the purpose of oxidation, storage, conversion or elimination. The stabilizing effect of the extract on insulin is both short and long term. It tends to prevent the rebound after the transitory action of insulin (6-8 hours) is over. The long term stabilizing or anchor effect may last for months—probably throughout the entire extract cycle. When the action of the extract is induced, a self limited and self determined long term symmetrical physiological action is inaugurated. The pattern once started tends to complete itself providing the factors affecting the blood sugar levels remain at all constant.

"In a word, the Macallum-Laughton extract is normally a stabilizing synergizing factor to insulin, an antiinsulin resistant, an antagonist to the anterior pituitary tending to anchor the blood sugar to normal levels and maintain its stability. In diabetes, it may be administered per orem alone or in combination with insulin and, by its action, it overcomes the insulin resistance and impaired utilization of hypophyseal diabetes and maintains a normal blood sugar level in prolonged symmetrical patterns with or without insulin for months. The extract action as shown by the primary, secondary and tertiary extract effects on utilization, the amplitude of the tolerance curves and the depression of the basic glycemia indicates its mode of operation."

Clinics on Secondary Gastro-Intestinal Disorders; Reciprocal Relationships. By Dr. Julius Friedenwald, Dr. Theodore H. Morrison, and Dr. Samuel Morrison. Price, $3. Pp. 251. Baltimore: William Wood & Co., 1938.

Symptoms interpreted by the patient as arising within the abdomen, generally in the stomach, occupy a large part of any practitioner's time. That such symptoms may not necessarily indicate a disorder of the organ designated by the patient is not a new idea. Neither is the opposite proposition startling: that symptoms may be induced elsewhere than in the gastrointestinal tract by disease of the latter. The attempt of the authors of these clinics has been to systematize and explain the production of gastrointestinal symptoms by disease processes in other parts of the body, and vice versa.

The first clinic contemplates the "relationship of gastrointestinal and cardiac affections." Perhaps the most common abdominal symptom experienced by the patient with cardiac disease is flatulence. Unfortunately this clinic does not do much to enlighten the reader about the origin, or for that matter the dissipation, of the gas. Flatulence is mentioned as a frequent symptom of unrecognized decompensation; but one wonders how frequently physicians of ordinary acuity fail to recognize a failing heart from other evidence than gas. The authors describe cardiac symptoms provoked by gastrointestinal dysfunction, two examples of which are anginal pain and arrhythmia. The type of arrhythmia that may be produced is not mentioned; but it is pointed out (page 9) that gastric stretching "inhibits the action of the vagus and is thus a potent cause of cardiac disturbance." This is obviously contrary to the usual physiologic and pharmacologic experience and is rather typical of interpretations of neurologic reactions throughout the book. The authors attempt fine distinctions between angina pectoris and a pseudoangina provoked by overeating or eating otherwise indiscreet. It is not suggested, how-

ever, that a heart with incompetent coronary circulation may be incapable of the effort incident to digestion on a large scale. In fact, it is not apparent in the presentation whether the authors think that cardiac symptoms arising from gastrointestinal disturbances, such as gas, occur only in diseased hearts or whether they think such symptoms can be induced as readily in perfectly normal ones. Many cardiologists will argue that cardiac symptoms, for example, angina, dyspnea and arrhythmia, after indiscretions of eating or associated with flatulence, are good evidence of cardiac disease. Several rather frequent sources of cardiac symptoms are not mentioned: esophageal diverticula and diaphragmatic hernias, for instance.

On the other hand, in a clinic on the relations of the stomach and the intestines the authors do much better, threading their way adroitly through the maze of chronic appendicitis, to come out neutral. Curiously they omit any mention of regional enteritis.

The old vagueness recurs in the clinic presenting the endocrinopathies. One is discouraged by the summary of Addison's disease, in which a discussion of the role of hypochloremia and potassium intoxication in the genesis of the typically severe abdominal symptoms is strangely lacking. Really humanitarian work could be done in this field, for on many patients with adrenal insufficiency exploratory procedures are done in the hot summer months for "gall stones," "bowel obstruction" and other conditions.

Perhaps the titling of the book as "Clinics" justified in the authors' minds the dogmatic and occasionally inaccurate presentation. The work fails to fulfil the expectations of the reader who seeks a serious analysis of obscure symptom formation.

Angina Pectoris: Nerve Pathways, Physiology, Symptomatology and Treatment. By Heyman R. Miller, M.D. Price, $3.25. Pp. 275. Baltimore: The Williams & Wilkins Company, 1939.

This book is primarily intended to present a pictorial representation of the autonomic nervous connections of the human heart. The purpose of these pictures is to make clear the pathways for the radiation of the pain of angina pectoris and the possible sites for a surgical attack on this syndrome. Such a purpose is certainly laudable, and the drawings and their legends are admirably done. Unfortunately, the author has also included a discussion of his conception of the pathogenesis and the therapy of angina pectoris. The author's view of pathogenesis is best quoted from page 7: "We prefer, therefore, to consider angina pectoris a paroxysmal upheaval (of the autonomic nervous system) of central origin, and this whether the individual has normal or abnormal coronary vessels. Excepting the sequelae of cardiovascular damage, the train of events following a sudden coronary occlusion is but one form of this paroxysmal upheaval." To the reviewer the second sentence cited *implies* that the occlusion of a coronary artery is simply one type of stimulus for the central upheaval. This relationship is not strictly drawn, however, and nowhere else in the book is specific mention made of any other stimulus for this outburst of autonomic activity. Nor is there any clear statement as to whether or not this outburst could be purely of central origin, as is an epileptiform attack. Tacit rejection by the author of a unitary origin for the attack of angina pectoris leads to the frequent, though undefined, use of the terms "coronary angina pectoris" and "noncoronary angina pectoris." This belief in the central origin of the anginal attack is reminiscent of the early views of Laennec and others; views which are usually considered definitely passé.

The author's ambivalent thinking is also apparent in the sections devoted to therapeutics. In describing the medical management of an attack of angina pectoris, the author writes as if the attack were due to occlusion of a coronary artery, rather than to a central upheaval. A bizarre group of drugs, 105 in all, is advocated for treatment. In the discussion of the diuretics one finds (page 188): "Some endocrine products are known to possess a diuretic action, the pituitary extracts (0.5-1 cc.) in diabetes insipidus, etc. . . . Their use, however, is quite exceptional." One might even say it is quite exceptionable. The author is enthusi-

astic about surgical procedures, particularly those that interrupt the sympathetic nervous connections of the heart. He does not consider the loss of pain as danger signal to be of any consequence, for he thinks that other symptoms of the upheaval of the autonomic system (for example, angor animi and sweating) "may carry the same weight as a danger or warning signal."

Cardiovascular Diseases: Their Diagnosis and Treatment. By David Scherf, M.D. and Linn J. Boyd, M.D., F.A.C.P. Price, $6.25. Pp. 458. St. Louis: The C. V. Mosby Co., 1939.

This book covers the most important problems in connection with cardiovascular disease in a more concise form than is usual in standard textbooks. The views expressed are based on the authors' personal experience, and no bibliography is appended. The views are not in discordance with generally accepted trends of thought. Two contributions to the value of the discussions are: first, the deliberate attempt to explain the underlying disturbances of physiology responsible for the clinical manifestations encountered in various abnormal cardiovascular states, and, second, the emphasis placed on the evaluation of data acquired at the bedside rather than through instrumental aid—information which might not always be available to every physician.

The initial chapters are devoted to the discussion of the mechanism and the differential diagnosis of dyspnea, as it occurs under various conditions, and of other clinical manifestations of cardiac failure. Special emphasis is devoted to the phenomenon of paroxysmal nocturnal dyspnea.

The remaining chapters deal with the conventional pathologic lesions affecting the heart and the peripheral vascular system, with extracardiac factors which eventuate in cardiopathies and with functional disturbances related to the cardiovascular apparatus. Therapeutic procedures employed in the various fields of cardiovascular disease are discussed in considerable detail. The derivatives of purin receive wide consideration and it is the authors' belief that relatively large doses should be administered in a short period of time in order to achieve satisfactory diuresis in cases of congestive heart failure.

The authors must be complimented on the straightforward manner in which their views are presented. Their book contains much valuable information, and while it is not intended to be a textbook in the ordinary sense of the word it is well worth reading by all who are concerned with the problems of cardiovascular disease.

Letters à un jeune praticien, sur les maladies de l'anus et due rectum. By Roger Savignac. Préface de Gosset. Paper. Price, 26 francs. Pp. 130. Paris: Masson & Cie, 1937.

The author has had approximately twenty years' experience in the Surgical Clinic of Salpêtrière as a consultant for diseases of the anus and rectum. Personal impressions gained from such clinical experience have been incorporated in this volume.

The importance of the examination of the anus and of the rectum is discussed, with the instruments used and the technic. He believes such an examination is indispensable in certain cases. The discussion of carcinoma of the rectum reveals an attitude of pessimism as to the general prognosis of such a condition. Surgical intervention is mentioned as the only curative form of treatment available. The beneficial effect of radium is mentioned. This phase of the subject is probably not in accordance with certain incorrect views in this country. He correctly emphasizes that roentgen and radium therapy are important methods in the management of carcinoma of the rectum and anus in certain cases.

The letter dealing with *recto-colites graves* discusses the general clinical features of the disease known as chronic ulcerative colitis in this country. A considerable portion of the discussion has to do with medicated instillations in the form of flushes. The discussion of hemorrhoids emphasizes the importance of the injection treatment in the early mild stage of the condition. Treatment of hemor-

rhoids and anal fissure by electrocoagulation seemed to produce satisfactory results in certain cases. There is considerable discussion about the diathermy treatment of rectal stricture.

The book is written in a free, informal style and made up of a series of letters addressed to "my friend." It contains no bibliography or photographs. Such a volume should have a limited appeal, for the remarks are general and detailed discussion has been omitted. It should be read by those who enjoy a general discussion of diseases of the of the anus and rectum.

Sex and Internal Secretions: A Survey of Recent Research. By Edgar Allen, Charles H. Danforth and Edward A. Doisy, editors. With a foreword by Robert M. Yerkes. Second edition. Price, $12.00. Pp. 1,346, with illustrations. Baltimore: Williams and Wilkins Co., 1939.

The introduction to this volume states that the book deals prodominantly with the subject of the mediation, by hormones circulating in the blood, of the sexual characteristics which are especially characteristic of the vertebrates, including man. It is impossible adequately to present a review of this more than 1,300 page book in the form of an abstract, because the editors have painstakingly examined all phases of published work dealing with an increasingly complex subject, and have presented them clearly and with essentially irreducible brevity. Fundamental subjects necessary to complete understanding of the whole subject, such as "cytological and genetic bases of sex," "embryonic development of sex," "modification of development of sex"' and "sex and secondary sex characters" are considered in section A, which precedes the chapters dealing with topics perhaps more familiar to the general reader.

The second division of the book is concerned with the physiologic aspects of the sexual glands, germ cells and accessory organs. An example of the comprehensiveness of the book is chapter 8, on the "endocrine function of the ovaries," which consists of 143 pages of discussion based on a bibliography of more than 700 references.

Section C deals with the "biochemistry and assay of gonadal hormones." Section D is on the "hypophysis and the gonadotropic hormones of the blood and urine in relation to the reproductive system."

The concluding chapter contains, among other things, material on the "relation of the vitamins to sex glands."

In this book may be found the careful compilation of data related to the subject that will enable student, teacher and investigator to review thoroughly what is known about sex and internal secretions at the present time.

The General Tissue and Humoral Response to an Avirulent Tubercle Bacillus Including Growth Characteristics of the Organism. By Sol Roy Rosenthal. Paper. Price, $2.50. Pp. 184, with 80 illustrations. Urbana, Ill.: University of Illinois Press, 1938.

This book reports work done on certain phases of growth of B C G and on the response of the tissues and blood of the guinea pig to B C G given by different routes.

The organism was found to have a cycle of growth resembling that previously described for the virulent tubercle bacillus, with passage through a granular phase. There was no reversion to virulent form in this work.

Tissue response was judged by alterations found in the reticuloendothelial system of body organs with sacrifice of the animals at various periods. This response varied from slight swelling of the cells to increase in number and further to grouping of the cells, often in characteristic tubercles. This reaction was limited variously in time and extent and then regressed.

The report is in monographic style and has a good bibliography. The descriptions of tissues are clear and convincing. Repetition of the many complete descriptions of fairly similar content makes for monotony but undoubtedly adds to the factual value of the report. Criticism may be made of the subjective standard of judging the lesser tissue reactions unless sections are described as complete

unknowns intermingled with controls. Blood cell studies in the guinea pig suffer from the marked normal variability of white cell content.

This thorough type of work supplies needed knowledge of the extensive participation of the reticuloendothelial system in the reactions to B C G. The inference that the reticuloendothelial system reaction is an immune type of response may still be held sub judice.

La medicine d'urgence: Symptomes, diagnostic, traitement immediat, formulaire. By J. Oddo, M.D. Seventh edition. Paper. Price, 120 francs. Pp. 840. Paris: Gaston Doin & Cie, 1939.

The popularity of this book is indicated by the necessity for the publication of another, the seventh, edition. The original edition appeared in 1910. This edition is similar to the preceding one, although modifications have been made in order to conform with present day ideas concerning physiology, symptoms, signs and treatment of emergency conditions. The major alterations were made in the chapters on acute cardiac insufficiency, epilepsy, hysteria, chronic hepatitis and nephritis. The book still contains many prescriptions which probably have no more effect than placebos. The author continues to use bloodletting in many conditions in which the rationale for this procedure may be questioned. The use of purgatives containing mild mercurous chlorides, even in the presence of uremia due to primary renal disease, is still recommended.

However, in spite of the fact that the reader may not agree with the author in regard to some of the recommended treatment, the book should be helpful in many respects. Such discussions as those of the abnormal physiology, pathogenesis, symptoms and other aspects of disease are brief and clear and should prove of value. The book covers an extensive field and includes most of the conditions that require immediate attention. Therapeutic methods in emergencies have always interested the clinician, while, even more, European ideas of treatment in these emergencies quite often are of particular concern to American clinicians.

The reviewer considers the book worthy of a continued place among the present day clinical books.

Introduction to Ophthalmology. By Peter C. Kronfeld, M.D., Professor of Ophthalmology, The Peiping Union Medical College. Price, $3.50. Pp. 331, with 37 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1938.

Kronfeld has made a very valuable contribution to facilitate teaching in ophthalmology. This volume is concise but thorough.

A number of diseases of the eye are not discussed in the general text, but they are described briefly in the index. Details of diagnosis and of examination are not included; instead, the author stresses the physiology and the pathogenesis of the physiologic and pathogenic factors in diseases of the eye. One chapter is an interesting discussion on the physiology of the retinal circulation. Another is a comprehensive survey of the visual pathway. The author stresses the importance of a thorough knowledge of the anatomy in making a differential diagnosis of intracranial lesions.

Principles are stated clearly in a more or less conversational way, making the book differ from the majority of textbooks. The author limits his recommendations for treatment to methods which he considers thoroughly tried. There is a bibliography at the end of each chapter.

This book is highly recommended as an adjunct to any study of ophthalmology.

Anatomic Factors in Hemorrhoids and Varicose Veins of Lower Extremities. By G. N. Alexandrov. Paper. Price, 27.50 kopecks. Pp. 109, with 64 illustrations. Samarxand, 1938.

This little volume is the result of painstaking anatomic postmortem dissections of venous trunks in 30 human cadavers: 20 with hemorrhoids and 10 with varicose veins. The dissections included the sites of dilated veins as well as the pelvic and thoracic veins.

These studies show that the pathologic dilatation of veins is due to a congenital maldevelopment of the venous system, a lack of adequate anastomoses between the three venous systems: portal, cava inferior and azygos-hemiazygos. Thus, the real cause of disturbance lies much higher than the site of lesion. This maldevelopment of anastomoses occurs in 3 to 5 per cent of normal people. It is in this group of people that hemorrhoids and varicose veins develop. The malformation can be explained on embryologic and phylogenetic bases.

The illustrations, though quite inexpensively reproduced, are adequate. The literature embraces 119 Russian and 43 European sources. The volume is of considerable interest to an anatomist as well as to an inquisitive surgeon.

Endocrinology in Modern Practice. By William Wolf. Second edition. Price, $10. Pp. 1077, with 189 illustrations. Philadelphia: W. B. Saunders Company, 1939.

In a review of the first edition of this book several years ago it was suggested that this was probably the best brief text on endocrinology yet produced. The second edition seems to maintain the same position. Endocrinology is a complex subject in a state of rapid flux. It is practically impossible to cover all its aspects authoritatively or adequately. But a vast amount of useful information is assembled here between two covers, and the illustrations and tables are especially valuable. For the clinician good summaries of anatomic and physiologic observations not readily accessible in most textbooks are assembled. There are some controversial points, especially in connection with current work on pituitary extract and sex hormones, but on the whole this book represents a sound appraisal of the subject.

Medical Jurisprudence and Toxicology. By William D. McNally. Price, $3.75. Pp. 386, with 37 tables. Philadelphia: W. B. Saunders Company, 1939.

The reviewer is most favorably impressed with this book, which seems to contain within reasonable compass the essential factors of medicolegal medicine. The first sections deal with such matters as signs of death, injuries, gunshot wounds and blood stains. In the later chapters drugs and poisons are discussed. The material is well arranged, and there are many references and an index.

News and Comment

The American College of Physicians.—The twenty-fifth annual session of the American College of Physicians will be held in Boston, April 21-25, 1941, with general headquarters at the Statler Hotel.

Dr. William B. Breed, of Boston, is general chairman of the session and will be in charge of the program of clinics and demonstrations in the hospitals and medical schools and of the panel and round table discussions to be conducted at the headquarters.